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THE EFFECT OF THE RICE-FRUIT DIET ON THE COMPOSITION OF THE BODY*

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THE development of effective therapeutic measures for the control of essential hypertension is one of the most pressing problems facing present-day medical investigators. Attempts to treat hypertension by various dietary measures have often stimulated the hopes of the medical profession,[1] but no dietary technic has, in fact, provided a means of breaking the therapeutic impasse.

The introduction of the rice-fruit diet in 1944 constitutes the latest attempt to control hypertension by dietary means. By the use of the diet, its originator reported significant lowering of the blood pressure in 62 per cent of 500 patients with essential hypertension; he also reported marked improvement in the eyegrounds, reversal of abnormal electrocardiographic patterns and diminution in the size of the heart in many of his patients.[2] The diet caused loss of body weight in most of the patients, mainly, according to Kempner,[2] because of diminution in "visible and invisible edema." In his hands, the diet did not induce negative nitrogen balance although it provides a daily intake of only 20 gm. of protein, all of which is from vegetable sources.

Since the appearance of Kempner's earlier articles, almost all his claims for the diet have been questioned by other investigators. Some observers doubt that the diet exerts a specific depressor effect on the blood pressure in patients with hypertension.[3] It has been shown that, in some patients at least, the diet induces negative nitrogen balance,[4] and the suggestion that the diet is, in reality, a semistarvation regimen has repeatedly been made. The occurrence of the salt-depletion syndrome in some patients receiving the rice-fruit diet has recently been held to indicate a need for discrimination in the therapeutic use of the measure.[5]

The controversy concerning the therapeutic usefulness of the rice-fruit diet is of considerable importance to the physician who must prescribe for patients with hypertension. He can hardly ignore the fact that many, and perhaps most, patients find the stringent requirements of the rice-fruit regimen almost impossible to fulfill over long periods. Nor can he fail to be concerned over the possibility that such a borderline diet is, under some circumstances, as dangerous as the hypertension it is supposed to alleviate. If the diet has no specific effect on the blood pressure in hypertensive patients, its use in the treatment of the disease should be abandoned forthwith. On the other hand, if it does, in fact, provide relief to patients with hypertension, some means of limiting the deleterious effects of the measure and of improving its palatability should be sought.

The basic information necessary for a decision in these matters does not appear to be available. It is obviously inadequate, for purposes of evaluation, to limit inquiry to the effect of the regimen on the blood pressure alone. Such a drastic dietary limitation is almost certain to produce important changes in body composition that, in turn, may determine whether or not the diet is therapeutically practicable. In planning the following study this fact was taken into account, as was the possibility that careful examination of the changes in body composition induced by the rice-fruit regimen would throw some light on the effective feature of the diet.

METHOD

Eight male patients with well established, moderately severe essential hypertension were selected for the study (Table 1). All had more or less incapacitating symptoms, of which headache was the most frequent, but none had an elevated blood urea nitrogen or other signs of renal insufficiency. Four of the 8 men complained of dyspnea on exertion (in 2 it was the chief complaint), but none had frank congestive failure.

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The patients were quartered in a special ward set aside for the study. Under these arrangements it was possible to maintain strict dietary control at all times. The patients were required to remain ambulatory throughout the experiment.

Basically, two diets were employed. The standard hospital diet provided 3000 calories, 100 gm. of protein, 150 gm. of fat and 8 to 12 gm. of sodium per day. The rice-fruit diet as used in the study supplied slightly more than 2000 calories, 22 gm. of vegetable protein, 3.3 gm. of vegetable fat and about 20 mg. of sodium per day. Daily supplements of vitamins A, D, thiamine, riboflavin, niacin and calcium pantothenate were given while the patients were on the rice-fruit diet. The addition of sodium-free protein was achieved by the use of a milk powder from which almost all the sodium had been removed by dialysis.* Sodium chloride was administered in the form of capsules containing 5 gm. each.

Table 1. *General Information on 8 Male Hypertensive Subjects.*

Subject	Age	Resting Blood Pressure on Entry	Duration of Hypertension	Eye-ground Changes	Symptoms
	yr.		*yr.*	*grade*	
L. A.	46	166/110	6	I	Headaches and dizziness
K. M.	40	186/136	6	I	Headaches, dyspnea and weakness
H. H.	58	190/120	9	II	Headaches and dyspnea on exertion
A. B.	44	180/106	4	II	Headaches and dyspnea on exertion
C. M.	32	198/132	4	III	Headaches, and numbness in right arm and leg
J. M.	53	224/134	3	II	Headaches, and dyspnea on exertion
C. P.	31	190/120	3	III	Headaches, and dizziness and loss of vision in left eye
G. R.	34	196/132	4	I	Headaches

Measurement of the basal blood pressure was carried out on alternate days between 7 and 8 a.m., before the patients had arisen and often before they were fully awake.

Twenty-four-hour urine specimens were collected daily, and the twenty-four-hour excretion of urinary chloride was measured three times weekly. The blood urea nitrogen was also determined three times weekly.

For the measurement of the specific gravity and of the total fat of the body, the methods described by Behnke, Feen and Welham,[6] Rathbun and Pace[7, 8] and Morales et al.[9] were employed in 6 subjects. These methods require measurement of the weight of the body in air, on the one hand, and the weight of the body under water, on the other. From these values, the volume displacement of the body can be calculated if the amount of residual air in the lungs is known. The latter was measured by means of the open-circuit technic.[10] Since the specific gravity of the body (body weight ÷ volume displacement) varies inversely with its fat content, an approximation of the weight of total body fat can be made once the specific gravity has been determined. The extracellular fluid volume and plasma volume were estimated by the thiocyanate method and the Evans blue dye technic, respectively.

From these key measurements it is possible to calculate the approximate composition of the body in terms of weight.[11] The bones are known to account for about 4 per cent of the normal adult body weight, and this figure was used in the present calculations. It is assumed, on reasonably good evidence, that under the conditions of these experiments, any change in body weight that may have occurred as a result of demineralization of the bones was relatively insignificant. The weight of the inactive tissue compartment is calculated as follows: weight of fat plus weight of bones plus weight of extracellular fluid. When the weight of the inactive compartment is subtracted from the total body weight one obtains an approximate value for the weight of active body tissue. This compartment is composed mainly of muscle tissue but includes small amounts of other tissue components (for example, fibrous and glandular tissue).

Other studies included electrocardiograms, 6-foot roentgenograms, retinal photographs and cold-pressor and Sodium Amytal tests, all of which were carried out during the control periods and at the end of the main test periods.

Table 2. *Duration of Control and Test Periods.*

Subject	Control Period	Period on Rice-Fruit Diet	Period on Rice-Fruit Diet Plus Protein	Period on Rice-Fruit Diet Plus Salt
	days	*days*	*days*	*days*
L. A.	43	42	14	22
K. M.	43	42	14	22
H. H.	25	42	17	—
A. B.	38	46	14	22
C. M.	44	102	—	—
J. M.	43	50	42	—
C. P.	54	23	—	—
G. R.	43	22	—	—

The order of the experiments was not constant in all the subjects but invariably included a prolonged control period, during which the standard hospital diet was given, and a test period, during which the unmodified rice-fruit diet was employed. The effect of adding sodium-free protein to the rice-fruit diet was studied in 5 subjects, and the effect of salt supplements (10 gm. daily) in 3. The times allowed for the various phases of the experiment are shown in Table 2. In 4 of the patients, the extreme monotony of the rice-fruit diet necessitated the substitution of a less rigid low-salt diet during

*Lonolac, supplies of which were furnished by Mead Johnson and Company, Evansville, Indiana.

a forty-day furlough from the hospital. This low-salt diet provided 2000 calories, 70 gm. of protein, 65 gm. of fat and about 400 mg. of sodium per day.

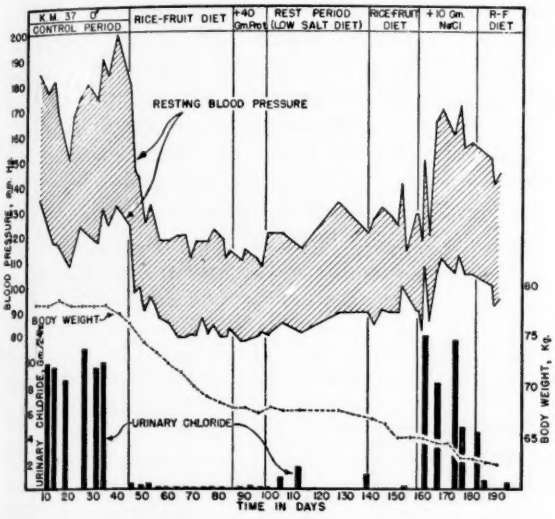

FIGURE 1. *Course of the Blood Pressure, Total Body Weight and Urinary Chloride Excretion in Subject K.M.*

When the patients returned to the hospital for the final phases of the study, the standard rice-fruit diet was reinstituted for a period of twenty days

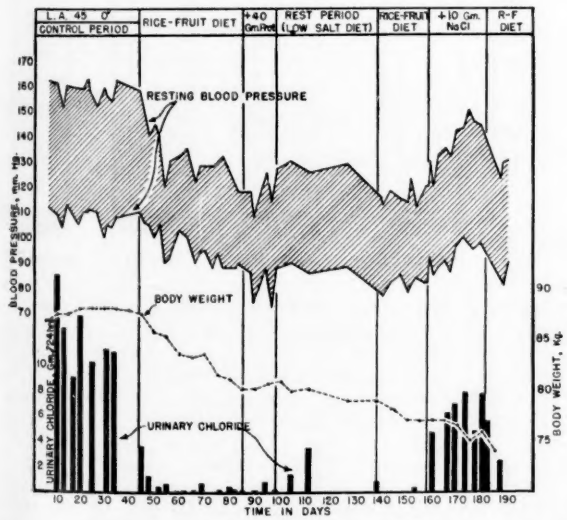

FIGURE 2. *Course of the Blood Pressure, Total Body Weight and Urinary Chloride Excretion in Subject L.A.*

before the use of salt supplements began (Fig. 1 and 2).

RESULTS

All the subjects complained of the extreme dietary restrictions made necessary by the regimen, but, in general, there was surprisingly little evidence of discontent during the experiments. One subject (C.M.) deviated slightly from the diet, and this may, or may not, account for the fact that his blood pressure remained unchanged throughout the experiments. The effect of the rice-fruit diet on the symptoms of which the subjects complained initially was salutary. Headache was markedly diminished or abolished in 6 of the 8 patients. There was less impressive improvement in symptoms other than headache. Electrocardiographically, there was no discernible improvement as a result of the use of the diet, but it should be noted that, apart from left-axis deviation, there had been no significant changes in the cardiograms initially. Two of the patients (H.H. and J.M.), who, at the beginning of the experiment, had moderate cardiac enlargement roentgenographically, showed definite diminution in the size of the heart after five weeks of treatment

TABLE 3. *Changes in Blood Pressure during the Rice-Fruit Diet with and without Salt (10 Gm. Daily) and Protein (40 Gm. Daily) Supplements.*

SUBJECT	AVERAGE BLOOD PRESSURE			
	FINAL CONTROL WEEK	FINAL WEEK OF RICE-FRUIT DIET TEST	FINAL WEEK OF RICE-FRUIT DIET PLUS PROTEIN	FINAL WEEK OF RICE-FRUIT DIET PLUS SALT
L. A.	158/110	118/86	120/84	146/98
K. M.	178/122	114/82	116/84	162/110
H. H.	194/126	186/118	188/122	—
A. B.	178/116	152/94	150/92	186/102
C. M.	202/126	192/120	—	—
J. M.	212/138	198/140	186/130	—
C. P.	198/126	154/94	—	—
G. R.	192/146	156/104	—	—

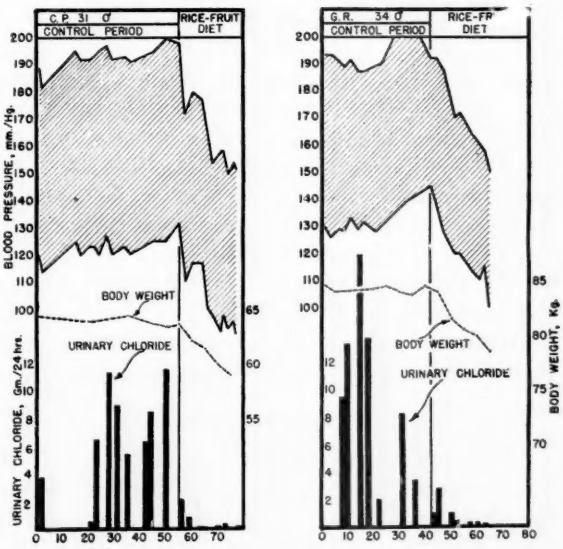

FIGURE 3. *Course of the Blood Pressure, Total Body Weight and Urinary Chloride Excretion in Subjects C.P. and G.R.*

with the rice-fruit diet. There were no ophthalmographic changes attributable to the diet in any of the patients.

The course of the blood pressure during the experiments is shown in Table 3 and in Figures 1-4.

Changes in body composition are summarized in Table 4. Figures 5 and 6 show the alterations in

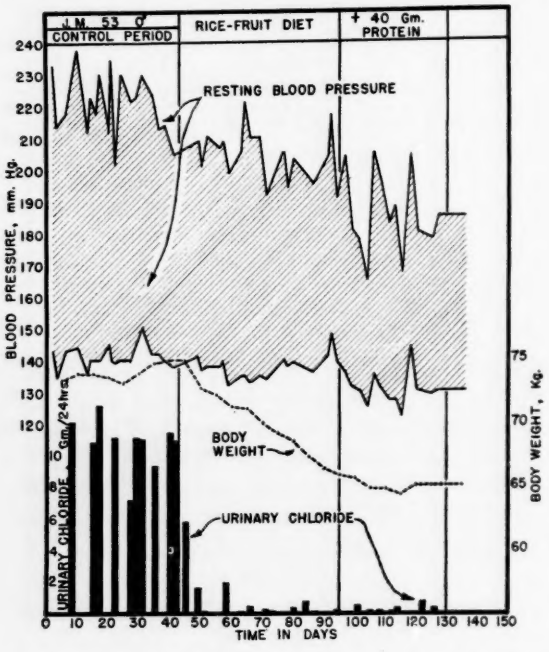

FIGURE 4. *Course of the Blood Pressure, Total Body Weight and Urinary Chloride Excretion in Subject J.M.*

body composition in 2 representative subjects (L.A. and K.M.). Not included in the tables or figures are the changes in plasma and blood volume which, although showing relatively little absolute change, tended to decline slightly.

Changes in the serum cholesterol levels during control and test periods are shown in Table 5.

DISCUSSION

There can be no doubt that the rice-fruit diet produces a decrease in the blood pressure of some hypertensive patients. It is known, of course, that hospitalization itself frequently causes a decline in the blood pressure of such patients. In the present study, however, there was no decrease in the resting blood pressure of the 8 hypertensive subjects after the first few days of the control periods. Day-to-day variations in the blood pressure, some of which were relatively large, were noted throughout the experiments but such changes were not systematic. Coincident with the institution of the rice-fruit diet there was an impressive decrease in the blood pressure of 4 of the 8 subjects. In 2 of the 4, the blood pressure returned to normal levels, and in the other 2 the levels were approaching normal when the experiments had to be discontinued. It may be true, as Kempner asserts, that in some patients the depressor effect of the rice-fruit diet does not become manifest for several months after its institution. It is possible, therefore, that significant responses would have been observed in more than 4 of the subjects had it been possible to lengthen the test periods. The addition of 40 gm. of sodium-free animal protein to the daily diet (in 5 subjects) did not affect the blood pressure. The depressor effect of the rice-fruit regimen was neither abolished nor enhanced by the measure, thus casting considerable doubt on the justification for the low-protein feature of the rice-fruit regimen. On

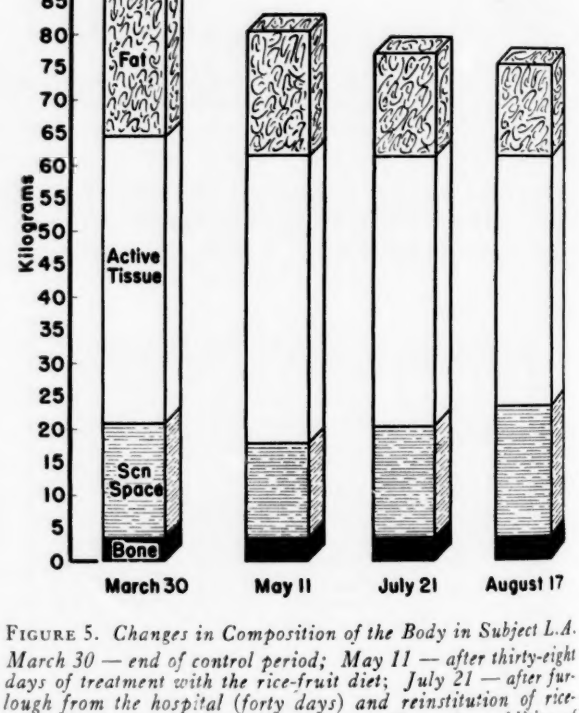

FIGURE 5. *Changes in Composition of the Body in Subject L.A. March 30 — end of control period; May 11 — after thirty-eight days of treatment with the rice-fruit diet; July 21 — after furlough from the hospital (forty days) and reinstitution of rice-fruit diet (eighteen days); and August 17 — after addition of salt to the rice-fruit diet.*

the other hand, the addition of 10 gm. of salt to the daily diet in 3 subjects produced a prompt rise in systolic and diastolic blood pressure, as well as a prompt return of unusually severe headache and other symptoms.

Common to all 8 subjects was a steady loss of weight, which began immediately after institution of the rice-fruit diet and continued, at the rate of about 1.5 kg. per week, until the diet was abandoned or modified. None of the subjects in the present study had visible edema, and determination of the

thiocyanate space during the control period indicated that only 1 of the subjects (H.H.) had a significant increase in the volume of extracellular fluid. Judging from measurements on 6 of the subjects, the rice-fruit diet invariably produced a marked decline in the extracellular fluid volume.

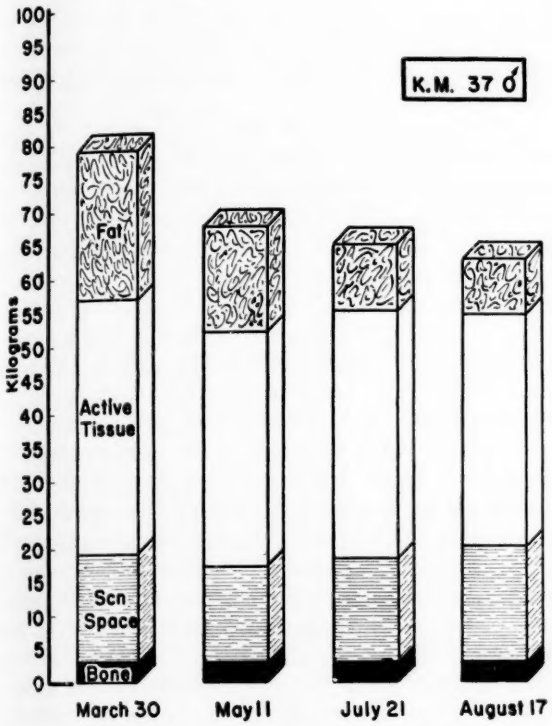

FIGURE 6. *Changes in Composition of the Body in Subject K.M.*

The significance of the dates is the same as in Figure 5.

was in the form of fat, and half in the form of extracellular fluid. Three of the subjects (A.B., C.M. and J.M.) lost significant amounts of active body tissue. These findings are similar to those obtained in normal young men by the use of a semistarvation diet[11] in that body fat and some active tissue were clearly consumed for the production of energy. They differed from those due to semistarvation in that the rice-fruit diet produced a definite decline in the extracellular fluid volume, a phenomenon that is doubtless attributable to the low-sodium content of the rice-fruit diet. Although Kempner's claim that the rice-fruit diet induces loss of "invisible edema" may, in some cases, be justified, there is unquestionably a loss of fat as well. Since many hypertensive patients are overweight, the loss of fat may be eminently desirable, but it is probably otherwise with the loss of protein. The loss of significant amounts of active tissue (presumably mostly muscle) by 3 of our subjects suggests that in some, if not in all, of the 8 subjects a negative nitrogen balance prevailed. The abrupt cessation of weight loss when salt-free protein was added to the diets (Fig. 1, 2 and 4) lends credence

TABLE 5. *Effect of Rice-Fruit Diet on Level of Serum Cholesterol in 7 Hypertensive Patients.*

SUBJECT	DAYS ON DIET	SERUM CHOLESTEROL		
		AVERAGE CONTROL VALUE	AVERAGE VALUE AFTER DIET	DECREASE PER CENT OF CONTROL VALUE
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*
L. A.	37	207	165	20.3
K. M.	37	267	153	42.7
H. H.	37	214	185	13.6
A. B.	37	236	107	54.7
C. M.	31	277	187	32.5
J. M.	31	236	182	22.9
C. P.	22	198	125	36.9

TABLE 4. *Changes in Composition of the Body in 7 Male Hypertensive Subjects Attributable to the Rice-Fruit Diet.**

SUBJECT	PERIOD OF OBSERVATION*	TOTAL BODY WEIGHT	SPECIFIC GRAVITY OF BODY	WEIGHT OF BODY FAT	THIOCYANATE SPACE	WEIGHT OF DRY BONE	TOTAL WEIGHT	
							INACTIVE	ACTIVE
		kg.		*kg.*	*kg.*	*kg.*	*kg.*	*kg.*
L. A.	Control	87.7	1.045	23.24	17.33	3.51	44.08	43.62
	RF 38	80.3	1.050	19.27	13.35	3.51	36.13	44.17
K. M.	Control	75.9	1.048	18.98	16.13	3.01	38.15	37.75
	RF 38	67.6	1.050	12.84	14.35	3.01	30.23	37.37
H. H.	Control	75.1	1.080	7.36	22.83	3.00	33.19	41.91
	RF 38	67.6	1.088	4.06	18.52	3.00	25.58	42.02
A. B.	Control	77.2	1.059	15.05	17.90	3.09	36.04	41.16
	RF 38	68.4	1.054	11.63	15.12	3.09	29.84	39.36
C. M.	Control	78.7	1.048	19.68	17.55	3.15	40.38	38.32
	RF 46	68.4	1.057	14.02	16.45	3.15	33.62	34.78
J. M.	Control	76.2	1.044	20.57	19.25	3.05	42.87	33.33
	RF 46	66.4	1.052	15.30	17.05	3.05	35.40	31.00
C. P.	Control	63.3	1.085	4.43	16.40	2.53	23.36	39.94
	RF 23	60.6	—	—	14.50	2.53	—	—
Average change of all patients		−8.55	—	−4.63	−2.69	—	−7.32	−1.23
Average change per week		−1.47	—	−0.80	−0.47	—	−1.28	−0.19

*The symbols RF 38, RF 46 and so forth indicate the number of days after the institution of the rice-fruit diet.

Just as striking was the loss of body fat. In thirty-eight days a typical subject (L.A.) lost a total of 7.4 kg. in body weight; of this amount, about half

to this view. Furthermore, it is not unreasonable to assume that any human subject receiving the rice-fruit diet begins to lose active body tissue in significant amounts if the diet is continued until the fat stores are exhausted.

Also common to all 8 of the subjects was the decline in serum cholesterol levels. This result, which was noted previously by Kempner[2] and by Schwartz and Merlis,[4] is at variance with the claim that serum cholesterol levels in the human being cannot be influenced by dietary means.[12]

Cold-pressor and Sodium Amytal tests before and during the test periods of the rice-fruit diet indicated that the diet induces a decline in reactivity in the hypertensive subject. The responses to the cold-pressor test were reduced by the dietary measure, but in no case did they become normal. Neither the cold-pressor nor the Sodium Amytal test enabled us to predict in advance which subjects would respond to the rice-fruit diet with a decrease in blood pressure.

The total effect, therefore, of the rice-fruit diet is to induce what amounts to semistarvation, as well as a decrease in the volume of extracellular fluid and a decrease in the serum cholesterol level. Whether or not any of these features is specifically and separately responsible for the depressor effect of the diet is not yet answerable with certainty. Semistarvation alone may cause a slight lowering of the blood pressure in normal persons,[11] and there is some evidence that it has a similar, but more marked, effect on hypertensive subjects. It seems unlikely, however, that anything short of frank starvation will cause the blood pressure in patients with severe hypertension to return to normal levels, and, in any case, semistarvation is a very dubious therapeutic tool. There remains to be considered the absolute decrease in the extracellular fluid volume. This feature is difficult to isolate, since it is extremely troublesome to prepare a genuinely low-sodium diet without also reducing the protein content to very low levels. The results of the present study suggest, however, that the diminution in extracellular fluid volume may in some way be related to the decline in blood pressure induced by the rice-fruit diet. If this is true, the treatment of essential hypertension by use of the rice-fruit diet can hardly be regarded as a fundamental therapeutic approach, since the disease is almost certainly not caused by alteration in the extracellular fluid volume. Furthermore, it is doubtful that a markedly decreased extracellular fluid volume can safely be maintained indefinitely.

The decline in blood pressure in the present study was therefore coincident with a decrease in total body weight, extracellular fluid volume, weight of body fat and serum cholesterol level and, presumably, with the institution of negative nitrogen balance. Return of the blood pressure to hypertensive levels, however, required an increase in extracellular fluid volume brought about by the addition of salt to the diet. The addition of salt-free protein to the diet for two weeks in 4 subjects and for 6 weeks in another did not cause a rise in blood pressure. It was not possible, because of the length of the experiments, to test the effect of addition of cholesterol to the diet, but there is no evidence, clinical or experimental, that cholesterol can, per se, exert a pressor effect.

Of what use, then, is the rice-fruit diet to the clinician? It seems clear that the diet will induce lowering of the blood pressure and amelioration of symptoms in some hypertensive patients. It will also induce rapid loss of body weight, a result that may be desirable in some cases.

On the other hand, it is known that severe sodium deprivation is decidedly dangerous in some hypertensive patients, especially in those with impaired renal function, and the use of the diet in such patients can only be classified as a desperate expedient. In hypertensive patients who are not overweight, the use of a semistarvation regimen of any sort makes little therapeutic sense. The semistarvation feature of the rice-fruit diet may be significantly modified by the addition of an adequate amount of protein, which, if provided in a sodium-free form, does not interfere with the depressor effect of the regimen. Finally, the use of the rice-fruit diet does not, in all probability, constitute a therapeutic weapon against the cause or causes of essential hypertension. The diet is of importance in that it provides the investigator with a relatively safe means of lowering the blood pressure for short periods in some hypertensive patients. To the clinician it provides a temporary means of relieving symptoms attributable to hypertension, but it is a measure that is dangerous in some patients and is curative in none.

Conclusions

The rice-fruit diet causes significant lowering of the blood pressure in some adult male hypertensive patients. In adult men the unmodified diet causes loss of body weight at the rate of about 1.5 kg. per week. The loss of weight is due mainly to loss of body fat and extracellular fluid volume. When the diet is continued over long periods, there is good reason to believe that a considerable loss of body protein occurs.

The addition of salt-free protein to the diet causes prompt cessation of weight loss but in no way interferes with the depressor effect of the diet. The addition of salt, on the other hand, causes prompt return of symptoms and elevation of the blood pressure in hypertensive subjects.

A rapid decline in the level of the serum cholesterol occurs in patients receiving the rice-fruit diet.

Use of the diet for short periods in hypertensive patients who are overweight and who have normal renal function may be justifiable. The use of the

unmodified diet over long periods is objectionable on theoretical grounds and may actually be dangerous.

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CARDIAC ARREST*

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Within the last decade there has been an increased effort on the part of surgical teams to recognize acute cardiac arrest on the operating table. There are very few emergencies that require such prompt treatment. Few patients can survive the anoxia produced by more than three minutes of cardiac standstill.[1, 2] To re-establish circulation within this brief period the anesthetist must recognize or suspect the condition and immediately notify the surgeon. It is preferable to be mistaken on many occasions than to lose time in a case of true arrest. The surgeon, if working in the abdomen or chest, must quickly check the lack of pulsations in the great vessels, and immediately proceed to reach the heart by whatever route is best for the particular case. He can then ascertain by palpation whether the heart is completely pulseless or whether it is fibrillating. In either event, it is of prime importance to re-establish and maintain efficient circulation by manual massage of the heart. As soon as this has been accomplished, there is no longer need for extreme haste, and attention may be given to the best methods available to restore the heart to normal rhythm if this has not already been established by the massage alone. During this period the anesthetist maintains artificial respirations by intermittent compression of the breathing bag. If the surgeon is working in the chest, the diagnosis of cardiac standstill is easily made, and massage of the ventricles performed, although the maneuver is more satisfactorily done through the left side of the chest. If abdominal surgery is being performed, the heart may be stimulated by compression through the diaphragm, but this method is so mechanically inefficient that the surgeon should at once proceed to open the left leaf of the diaphragm in order to compress the ventricles more effectively. Since many of the cases of cardiac arrest occur when neither the chest nor the abdomen is open, the surgeon should not hesitate to enter the left side of the chest through the fourth or fifth intercostal space as described by Lampson, Lincoln and Schaffer.[3] Johnson and Kirby[2] advocate cutting the fourth and fifth cartilages to give better exposure and allow more efficient massage if a rib spreader is not available.

Often, the surgical instruments may not be in the room, because the operation either has not been started or has been completed. A small kit with the few sterile instruments essential for entering the chest should always be in readiness on the same floor as the operating room. It need not be elaborate. The one in our operating room consists of 2 small retractors, 6 curved and 6 straight hemostats, 2 toothed forceps and 2 scalpels (Fig. 1). These are all placed in a small pan without sponges or towels (which might obscure the instruments and can always be obtained while the circulation is being re-established). Besides knowing what to do when cardiac standstill occurs, a surgeon should also be familiar with palpation of the heart, both through the chest and through the diaphragm. As Ruzicka and Nicholson[1] point out, the time to learn this is not when one is first faced with a case of circulatory arrest, and all surgical residents early in their training should be shown at the autopsy table how best to approach the heart for massage through the chest and through the diaphragm. The rate at which massage of the heart is most efficient has been investigated in dogs by Johnson and Kirby,[2] who found that the more rapid the rate the greater the

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blood flow. A rate of 120 times a minute was the most efficient but is too tiring unless there are two operators to alternate. However, a rate of 60 to 80 times a minute can be maintained without fatigue by one surgeon. They also found that compression of the heart between the thumb in front and the fingers behind produced twice as much blood flow as compressing the heart against the anterior chest wall and five times as much blood flow as compressing the heart from the abdominal side of the diaphragm without incising the latter. It is also interesting and not surprising that they found that it required a certain amount of practice before a really effective blood flow by cardiac massage could be maintained. Recently, Beck and Rand[4] have developed an apparatus whereby suction cups applied to the heart can maintain cardiac massage by mechanical means. They have incorporated this apparatus and a defibrillator into one machine.

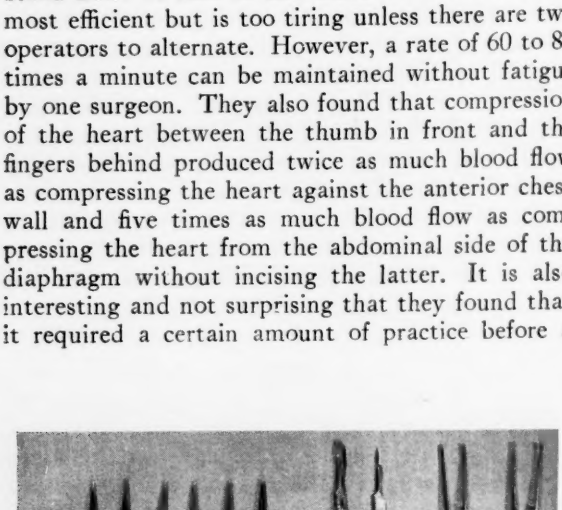

FIGURE 1. *Cardiac-Resuscitation Kit, Including Separately Wrapped Syringe with Temporarily Sealed Tip.*

If the heart does not resume a regular spontaneous rhythm within a short time and while the circulation is being maintained by manual compression of the ventricles, further treatment must be instituted. This varies, depending upon whether the heart is found in standstill or fibrillation. A detailed review of all the drugs that have been found useful as well as the rationale of serial defibrillation by application of an electric shock to the heart may be found in an exhaustive review by Wiggin, Saunders and Small.[5] The present opinion is that serial defibrillation is probably the most effective means of stopping ventricular fibrillation. However, even though the apparatus required is relatively simple, it is not as yet common equipment in the operating room. Procaine hydrochloride is also very effective in reducing the irritability of the conduction system of the heart and the myocardium, and if the heart is found fibrillating, procaine should be given intravenously in a 1 per cent solution in doses of 40 to 60 mg. Sometimes, therapy will convert the fibrillating heart to normal rhythm and sometimes to complete standstill. Whether the standstill was thus induced or was the condition originally responsible for the circulatory arrest, the treatment is the same. The manual massage will often be sufficient, but the heart beat will be strengthened by injection of 0.5 cc. of epinephrine, 1:1000 dilution, into a vein, the right auricle or ventricle. This amount should never be exceeded, and some[6] believe the amount should be even less. We have available a syringe containing 9.5 cc. of procaine 1 per cent and 0.5 cc. of epinephrine 1:1000 (Fig. 1). Some might consider these drugs as having opposing effects or as a "shotgun" combination, but when circulatory arrest occurs, one can rarely be sure whether cardiac standstill or ventricular fibrillation is the cause. Therefore, the epinephrine serves to stimulate a more forceful contraction while the procaine has a protecting effect against fibrillation so that the contractions will be co-ordinated. This syringe with a temporarily sealed tip and its contents, together with the emergency kit of instruments mentioned above, are kept in a cabinet in the central part of the operating-room corridor with a large sign on each side of the cabinet stating "Cardiac Resuscitation Kit." All operating-room personnel are familiar with its location and purpose, so that no time is lost when it is needed.

More and more reports are appearing in the literature of cases of acute cardiac arrest with complete recovery.[3, 7] To these we add the case reported below.

CASE REPORT

G. L. M., a retired 78-year-old clerk, was admitted to the hospital for the first time on May 4, 1949, complaining of a sudden attack of nausea, vomiting and right-upper-quadrant pain, which had occurred a few hours before. The pain had been temporarily relieved by vomiting. He had noted the day before that the stools were clay colored and the urine dark. He knew that his blood pressure had been above normal and that about 5 years previously he had suffered a so-called shock while working in his garden. After this he was paralyzed on the right side, and was unable to talk. He recovered entirely, however, in about 1 week.

Physical examination showed a mildly jaundiced man. The chest was clear. There was some spasm in the right upper quadrant of the abdomen, and a questionable mass was felt. By auscultation peristalsis was somewhat reduced.

The temperature was 102.8°F. by rectum, the pulse 100, and the respirations 24.

The white-cell count was 24,100, with 98 per cent neutrophils. The prothrombin time was normal. There was a trace of bile in the urine. X-ray study showed opaque shadows

suggesting a stone in the region of the gall bladder. A cardiac consultant gave the following opinion:

> Except for slight dyspnea on exertion and vague lateral chest pains, which are not associated with exertion, this patient has no cardiorespiratory symptoms. The heart appears to be slightly enlarged to the left; the rate is 76 and regular. There is a rough, Grade II systolic murmur, heard best at the apex on forced expiration and also at the second right intercostal space transmitted to the neck vessels. The aortic second sound is clear and loud and greater than the pulmonic. No diastolic murmurs are heard. There is slight pitting edema of the feet and ankles. The lungs are clear and resonant throughout. The blood pressure is 190/80. The diagnosis is hypertensive heart disease with a systolic murmur possibly due to dilatation of the aorta or to aortic stenosis. An electrocardiogram shows marked left ventricular hypertrophy and strain. The patient is not a very good operative risk, but at least he is not in cardiac failure.

Digitalis was given in preparation for operation.

A cholecystectomy and a choledochostomy were done on May 6, under endotracheal ether anesthesia. The patient withstood the operation well. The anesthesia was uneventful except for a fall in blood pressure from 260/100 to 140/80 immediately after the endotracheal tube was inserted. This was accompanied by an elevation in pulse rate from 80 to 100 and slight irregularity of the pulse was noted. Atropine, 0.6 mg. (1/100 gr.), was given intravenously, and the pulse soon became regular and stayed at a rate of about 100. The blood pressure returned to 220/110 and did not again fall lower than this level. The patient left the operating room in good condition, and his immediate recovery was uneventful. The pathological report was chronic cholecystitis and cholelithiasis.

Forty-eight hours after operation the patient was found with cold, clammy skin; he was complaining of burning pain under the manubrium. The heart rhythm was irregular, suggesting fibrillation. An electrocardiogram was suggestive of anterior infarction. The next day the medical consultant reviewed the electrocardiograms and stated that there was considerable doubt whether or not he had had a myocardial infarction. He believed that it was advisable to continue quinidine and digitalis and that the patient could start cautious mobilization. Slight abdominal distention was first noted on the 5th postoperative day and fluctuated considerably in degree during the next few days. A Miller–Abbott tube was passed, but because of persistence of clinical and x-ray evidence of small-bowel obstruction, re-exploration of the abdomen was done 11 days after the first operation.

The second operation was again performed under endotracheal ether anesthesia after induction with 8 cc. of Sodium Pentothal in 2.5 per cent solution. The course was uneventful except for a blood-pressure fall from an initial reading of 210/100 to 100/50 during the first ½ hour of anesthesia. This was before intubation and could not be satisfactorily explained. Three minims of Neo-Synephrine in 1 per cent solution was given subcutaneously, with restoration of the blood pressure to 140/80; the tube was placed in the trachea without difficulty, and the operation begun. When the abdomen was opened, the omentum was found attached to the bed of the gall bladder by fairly dense adhesions. The surgeon (W. G. S.) had just begun to free these adhesions, and was putting no traction on the mesentery when suddenly the blood pressure became unobtainable. At that moment the pulse was palpable at the wrist, but it disappeared while being felt, and within 20 or 30 seconds the respirations also ceased. The surgeon was immediately asked to feel for aortic pulsations, and when he confirmed that none were present he was encouraged to open the left leaf of the diaphragm. This was done, and the heart was found pulseless and flabby. The surgeon began to squeeze the heart rhythmically between his fingers and thumb at an estimated rate of 60 strokes per minute. During the time that the diaphragm was being opened, a syringe containing 9.5 cc. of 1 per cent solution of procaine and 0.5 cc. of epinephrine, 1:1000 dilution, was obtained. The contents were rapidly injected through a three-way stopcock in the intravenous tubing and pumped along by refilling the same syringe from the infusion bottle. Within 30 seconds of the time cardiac massage was begun, and about 1 minute after the injection, there was an occasional spontaneous contraction of the ventricles between the artificial strokes, and about 1 minute later, regular spontaneous rhythm was resumed. Within 30 seconds of the beginning of spontaneous cardiac action the pulse could be obtained at 80, and the blood pressure at 240/100. It was estimated that the cardiac standstill had lasted at least 3 minutes. Very shortly after the appearance of the pulse and blood pressure, spontaneous respirations reappeared at a rate of 20 per minute. Respirations had been artificially maintained by intermittent compression of the rebreathing bag, never exceeding a pressure equivalent to

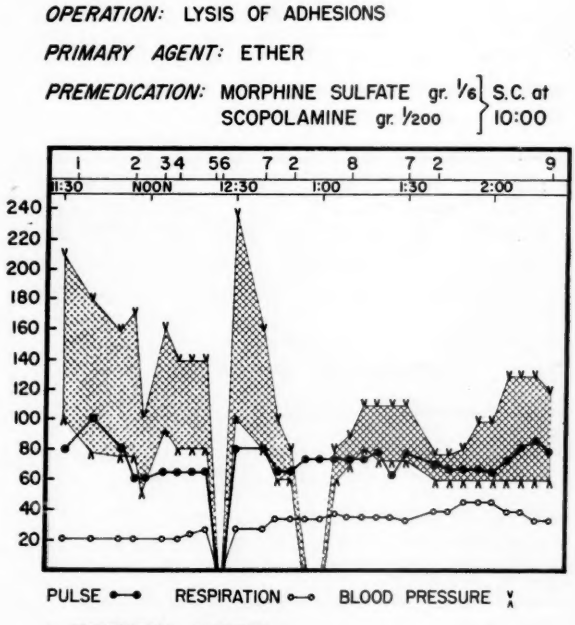
OPERATION: LYSIS OF ADHESIONS
PRIMARY AGENT: ETHER
PREMEDICATION: MORPHINE SULFATE gr. 1/6 } S.C. at
SCOPOLAMINE gr. 1/200 } 10:00
1 2 3 4 5 6 7 2 8 7 2 9
11:30 NOON 12:30 1:00 1:30 2:00
240 220 200 180 160 140 120 100 80 60 40 20
PULSE RESPIRATION BLOOD PRESSURE
1. ANESTHESIA STARTED
2. NEOSYNEPHRIN 1% 3 MINIMS S.C.
3. ENDOTRACHEAL TUBE INSERTED
4. OPERATION STARTED
5. I.V. 9 1/2 cc. PROCAINE 1%
1/2 cc. EPINEPHRINE 1:1000
10 cc. PROCAINE 1%
6. CARDIAC MASSAGE
7. 500 cc. WHOLE BLOOD STARTED
8. PULSE IRREGULAR
9. OPERATION ENDED

FIGURE 2. *Anesthesia Record.*

15 cm. of mercury on inspiration, allowing no positive pressure on expiration and maintaining expiration slightly longer in duration than inspiration. Since the obstruction of the small bowel was almost complete, it was considered imperative to continue the operation.

Within 10 minutes of the reappearance of the pulse and blood pressure, the latter fell to 160/80 and within another 5 minutes to 100/60 and the pulse became 65 per minute. Three minims of Neo-Synephrine, 1 per cent solution, was given subcutaneously every 20 to 25 minutes, but the blood pressure did not rise over 100/60 and at times fell as low as 70/50. The pulse, however, remained remarkably constant between 65 and 78 per minute. The respirations became a little more rapid, averaging about 36 per minutes. The variations can be followed on the anesthesia chart (Fig. 2). As soon as possible, the patient was connected to Lead 3 of the electrocardiogram, this being the only one that could be applied without contaminating the sterile field. It showed that he had a pure ventricular rhythm. A reproduction of this tracing is seen in Figure 3. A further recording of this lead was made every 10 minutes until the end of the operation, which continued for 2 hours after the cardiac arrest. At this time there was a lapse of ½ hour before all the leads of the electrocardiogram could be connected. By then sinus rhythm had returned, and the tracing was of essentially the

same pattern as that recorded preoperatively except for further depression of the segment in Lead V_5, suggesting further strain (Fig. 4). At this time the blood pressure had become more stable at 110/60, and the pulse, which had been irregular at times, was more regular, with a rate of 90. The operation consisted of freeing of dense adhesions, which had kinked the jejunum and caused complete obstruction.

At the end of the operation the patient's color was good, and the anesthesia had been lightened to such an extent that he was swallowing. The endotracheal tube was removed before he left the operating room, and a good airway was maintained with a pharyngeal tube. Three drains were in place at the end of the operation. The T tube, which had been placed in the common duct at the time of the first operation, was inadvertently displaced in the process of opening the left leaf of the diaphragm to massage the heart. This was

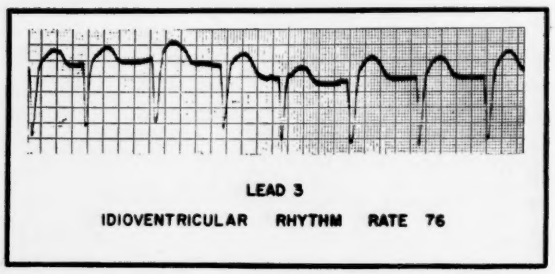

FIGURE 3. *Electrocardiographic Tracing Taken Thirty Minutes after Restoration of the Heart Beat.*

replaced by a simple catheter. This catheter and a cigarette drain in Morison's pouch were brought out through the stab wound to the right of the incision. The pleural space in the left side of the chest had been entered when the left leaf of the diaphragm was opened, and therefore a catheter was placed in the pleural cavity near the diaphragm and brought out through a stab wound in the left sixth intercostal space. This was thoroughly aspirated at the end of the operation while intermittent positive pressure was applied through the endotracheal tube. X-ray examination on the 3rd postoperative day showed the lung to be fully expanded. The catheter in the pleural space was removed at this time, and there were no pulmonary complications.

The patient was fully conscious and talking approximately 2 hours after operation, and at no time postoperatively was there any evidence that his mental processes were any different than they had been preoperatively. There was gradual improvement in his physical condition, and 3 weeks after the second operation, he was eating well and his stools contained a normal amount of bile. At follow-up visits on July 15 and again on October 14 he stated that he felt well, and the wound was well healed.

Summary and Conclusions

A case of cardiac standstill with complete recovery occurring in a seventy-eight-year-old man undergoing a lysis of adhesions for intestinal obstruction under endotracheal ether is presented.

It is emphasized that prompt recognition by the anesthetist and prompt action by the surgeon are necessary for successful therapy. The time available for restoring circulation without irreversible damage to brain cells is generally considered to be no more than three minutes.

All surgical residents should be taught at the autopsy table how best to approach the heart for massage through the chest and through the diaphragm.

It should be emphasized that cardiac massage from below the intact diaphragm against the chest wall is far less efficient than grasping the heart, through an opening either in the diaphragm or in the chest wall, and compressing it between the thumb and fingers.

The heart should be compressed at least sixty times a minute to achieve the most efficient blood flow.

A small emergency kit of instruments should always be present and plainly marked in a central position in the operating room in the event that there are no other instruments available when circulatory arrest occurs.

Electrical equipment for serial defibrillation should be ready if possible.

It is recommended that a syringe containing 9.5 cc. of procaine, 1 per cent solution, and 0.5 cc. of

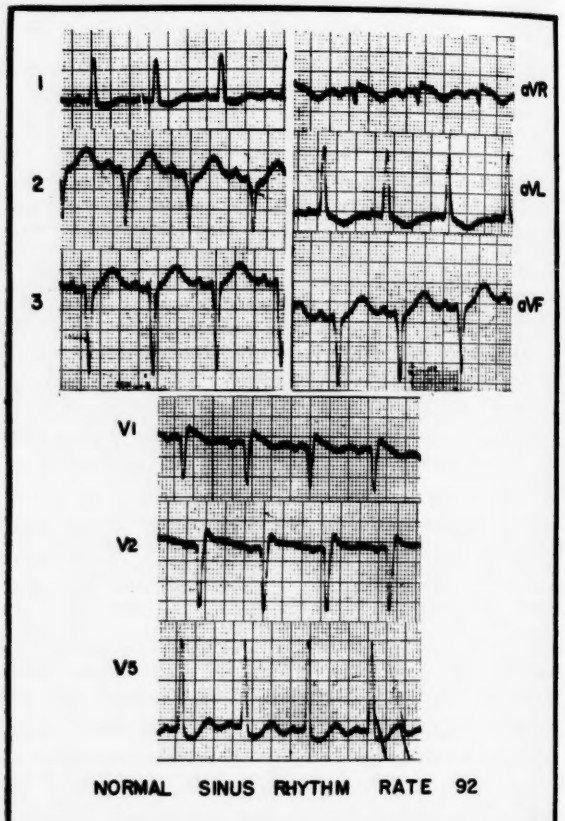

FIGURE 4. *Electrocardiographic Tracing Taken Two Hours and Ten Minutes after Restoration of the Heart Beat. There is no significant change from the preoperative tracing except for further depression of the ST segment in Lead V_5, suggesting further strain.*

epinephrine, 1:1000 dilution, always be available in a central location for intravenous or intracardiac injection.

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LIFE EXPECTANCY AND PROBABLE DISABILITY IN MULTIPLE SCLEROSIS*

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BOSTON

THE health problems presented by a disease differ decidedly as they are viewed from the standpoint of the community, and from that of the patient and his physician. The primary method of study is also different, for the population survey determines community effect and the clinical case history applies to the individual. The two objectives and the two methods, nevertheless, have common ground, and each contributes to the other. Clinical description provides the indispensable information of the disease, its nature and its course that is the basis for epidemiologic observations. The extensive data on general occurrence of the disease in population groups broaden the information to be had from clinical studies of the individual.

Knowledge of such rare diseases as multiple sclerosis is for practical reasons largely based on observations in hospitals, where numbers of patients are brought together with greater ease than in private practice. Hospital patients have the disadvantage that they often represent the fraction of existing cases with more severe manifestations, with the result that observations tend to be biased toward underestimation of frequency and overestimation of severity. Clinical judgment on the prognosis for recovery and for duration of illness has promise of greater reliability when it is reinforced by data on all forms and stages of the disease and on most cases in a community.

A field survey of multiple sclerosis was made in the Boston–Brookline area in 1949 as one of six similar studies in representative regions of North America. Methods of study, the frequency of existing cases (prevalence) and of new cases per year (incidence) are reported elsewhere.[1] The purpose was to assess morbidity and mortality of multiple sclerosis by age, sex, race and demographic relations and to compare the results with those of other areas within the continental United States. The data consisted of cases of multiple sclerosis recorded from 1939 to 1948 in hospitals and clinics, by practicing physicians and by official death registration. Each source of information had its particular value. The principal reliance for information of newly developed cases was the practicing physicians. Death certificates contributed to knowledge of cases originally studied in hospitals.

The frequency of occurrence of multiple sclerosis in different places at various periods and among fractions of populations is the primary concern of public health, and a function of epidemiologic analysis. The following considerations are of more direct interest to the patient with multiple sclerosis and to his medical adviser. The inferences drawn are from Boston experience, and will reflect especially the current behavior of the disease in the New England area.

Annual Occurrence

The community aspects of multiple sclerosis are expressed first in numbers of existing cases in a given community and secondly by the relative frequency of various clinical stages of the disease. From the data of the Boston survey the average annual prevalence was estimated as 51 cases per 100,000 population, with a marked sex difference since the rate for males was 37 and that for females 64 per 100,000. More cases occurred at the ages of thirty to thirty-five years than in any other age group.

The full impact of any chronic disease on a population is best understood when cases are classed according to degree of disability. Data on multiple sclerosis for Boston gave information on the status of the patient's activities at the time of last observation. Following the classification of Kolb[2] in a study of clinic patients with multiple sclerosis in Baltimore three categories of disability were distinguished. "Working full time" indicates that the patient was continuing his usual work, although effectiveness might well be less because of the disease. "Ambulatory" indicates a transitional state, with the patient unable to fill an employed position but caring for himself in daily life, despite longer or shorter periods of pronounced disability. "Bedridden" indicates essential total disability, with the patient dependent on nursing care at home, in an institution or in a hospital. The three degrees

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of disability represent increasing costs for medical care and a decreasing social usefulness. An economic weighting is not attempted.

Figure 1 presents the average annual distributions of cases by age, sex and degree of disability. Few patients with multiple sclerosis die in the course of a year (4 per cent of male and 3 per cent of female patients), but the majority have a disability of such extent that they are unable to work. A similar distribution of disability can be demonstrated for short periods and for many diseases, as during an epidemic, but the characteristic feature of multiple sclerosis is that the situation exists year after year. The patients who die in the course of a given year are replaced by new cases. There is a gradual exaggerated state of disability; some may improve markedly, but the condition of others is unexpectedly aggravated. The end result is that community needs for medical care of multiple sclerosis remain much the same. Total annual patients per 100,000 population are given in Table 1.

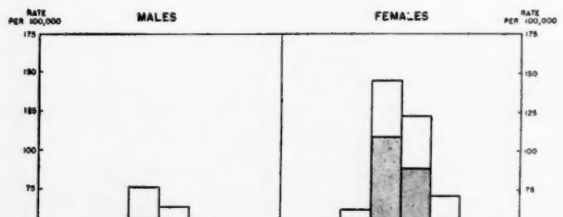

FIGURE 1. *Average Annual Cases of Multiple Sclerosis per 100,000 Population by Sex, Age and Degree of Disability (Boston Survey, 1939-1948).*

TABLE 1. *Cases of Multiple Sclerosis per Year per 100,000 Persons by Degree of Disability and by Sex.*

DEGREE OF DISABILITY	MALES	FEMALES	ALL CASES
Working full time	10.3	14.7	12.5
Ambulatory	16.9	35.1	26.0
Bedridden	8.6	12.9	10.8
Dead	1.3	1.8	1.5
Total prevalence	37.1	64.5	50.8

LIFE EXPECTANCY

The static situation that characterizes the community differs greatly from the progressive deterioration experienced by the individual with multiple sclerosis. The primary question of the patient is not of the number and state of his fellow sufferers but of his own fate in the years to come. Clinical judgment permits the physician to advise in many details, but with a disease of the long duration and relative rarity of multiple sclerosis, years of experience are necessary for a sound opinion on the expected course. The objective results of a statistical analysis of more cases than are usually seen by a single physician may serve usefully in prognosis and as a means for measuring therapeutic results of newly suggested methods of treatment.

The average duration of multiple sclerosis from onset to death can be estimated in several ways.

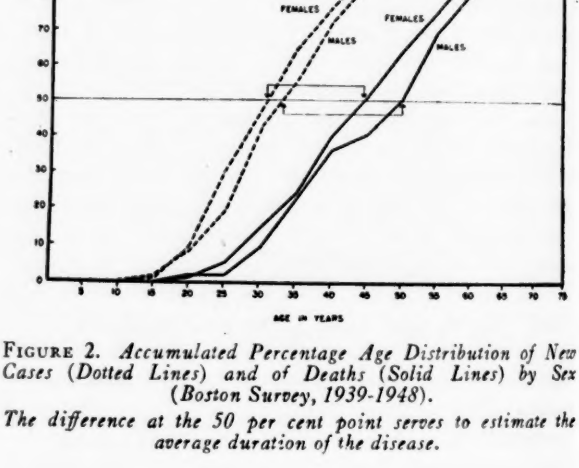

FIGURE 2. *Accumulated Percentage Age Distribution of New Cases (Dotted Lines) and of Deaths (Solid Lines) by Sex (Boston Survey, 1939-1948).*

The difference at the 50 per cent point serves to estimate the average duration of the disease.

One method (Fig. 2) relates the average age of the patients at onset of disease to the average age at death. Curves are drawn for both males and females, with the ordinates representing for the one set the percentage of persons who acquired the disease up to the age given by the abscissas, and for the second set the accumulated percentage of patients dying at a given age. The age difference at the 50 per cent point of the incidence and death curves gives the average duration of disease, which is seventeen and five-tenths years for males and fifteen and five-tenths years for females. Life expectancy is conceivably subject to considerable variation from the average, depending upon whether the disease first appears early or late in life. This

method cannot determine such variation. Furthermore, the estimate is open to error because incidence is based on cases occurring from 1939 to 1948, whereas deaths are from cases of earlier time.

A less direct, but also a less biased estimate, may be obtained if the data are treated by life-table technics. Details of the method are to be had in general treatises on life tables,[3] and especially those that emphasize their application to chronic disease.[4] The initial step is to calculate the mortality, at various periods after the onset of disease. Since age of the patient and duration of disease are both determining factors, the 784 cases were divided into broad groups according to age at onset. Annual mortality rates,* according to years of duration, averaged 3.98 per cent for males and 3.02 per cent for females. The difference between the sexes was most pronounced when the disease had lasted five to fourteen years, males then having twice the mortality of females. Differences were especially pronounced when the disease had started at about twenty years of age (males 7.0 and females 2.8 per cent). Patients acquiring the disease after forty-five years of age generally had a shorter life expectancy than those becoming ill at younger ages. Thus, sex and the duration of the disease are constant factors in determining mortality in any given year, whereas the age of the patient at onset first becomes significant in the fifth decade of life.

Computed mortality rates were next used to construct survivor curves at relevant ages (Fig. 3). The diagram compares the life curve for persons acquiring multiple sclerosis with life curves for white males and females of the United States, 1939–1941.[3] A cohort, or group of 1000 persons, was followed from birth to death, with the number of survivors at the end of each year plotted as ordinates. The upper heavy curve shows the average behavior of the normal population. Each of the four "descending branches" indicates the survivor curves for persons with multiple sclerosis, where the cohort acquired the disease at ages twenty, thirty, forty and fifty years respectively. The diagram for males differs from that for females mainly in the first age group, where males acquiring the disease at about twenty years of age are seen to die more promptly than females of that age. The life curves indicate no appreciable difference between the sexes when the onset of the disease is at the age of thirty years and over. If the age at onset is known, these survivor curves permit ready computation of life expectancy in terms of the median or average — namely, the number of years after onset when half the cohort is still alive.

*The author will supply detailed fatality tables to interested readers upon request.

Forecast of Degree of Disability

The anticipated progressive disability has equal importance with the expected duration of life. Cases were arranged according to degree of disability, by years after onset of disease. Three broad categories were used, — working, ambulatory and bedridden, — as well as the deaths that occurred.

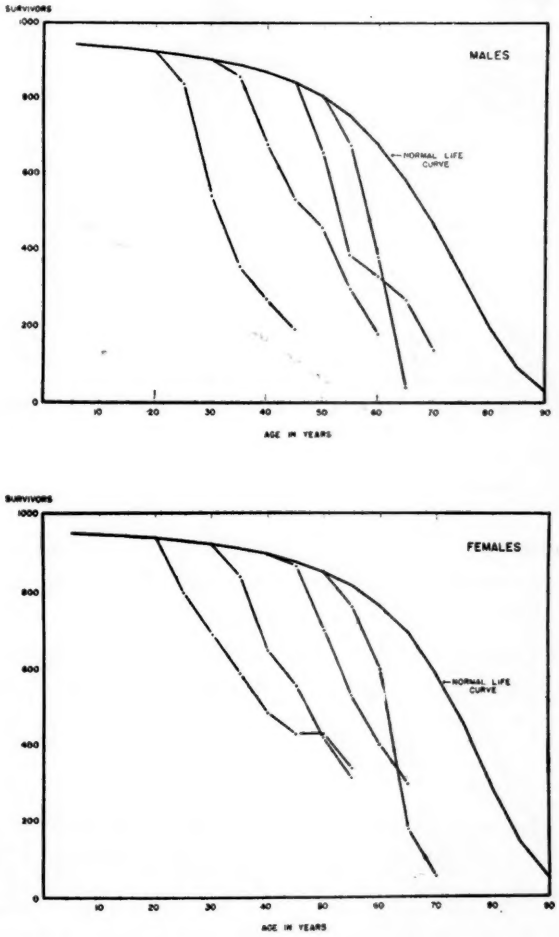

FIGURE 3. *Life Curves for Multiple Sclerosis by Sex. Normal curves of survivors of 1000 persons at increasing age are compared to curves of survivors, assuming that these persons acquire multiple sclerosis at the age of twenty, thirty, forty and fifty respectively.*

Figure 4 shows the average death and disability rates for male and female patients according to years after onset of disease. Distributions of survivors were then computed to represent degrees of clinical disease, existing at various years after onset.

Individual charts for each of the four groups, arranged according to age at onset (twenty, thirty,

forty and fifty years), naturally deviate from the average, which is illustrated in Figure 4. The differences are shown in Table 2, which gives median expectancies for the number of years after onset when half the cohort is dead (life expectancy),

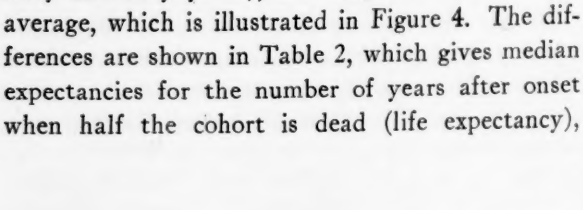

FIGURE 4. *Percentage of Survivors and Degree of Disability by Five-Year Periods after Onset of Multiple Sclerosis and by Sex (Males on the Left and Females on the Right).*
Computations are made on the basis of all patients in Boston, 1939-1948, regardless of age at onset.

when half the cohort is bedridden (expectancy for complete disability) and when half the cohort has ceased to work (work expectancy). The work expectancy could not be determined with greater exactness than "less than five years," since for all age groups more than half the patients had ceased to work within five years of onset.

For patients with multiple sclerosis, both functional prognosis and the prognosis for life are indicated by means of expectancies set forth in Table 2. Most patients will cease work within five years; after eleven to fourteen years they reach a state of total confinement to bed; and death occurs after 12 to 20 years. All expectancies are less when the disease is acquired after the age of forty-five years. Females, generally, have a better expectancy than males, especially with onset of the disease at about twenty years of age.

Multiple sclerosis is a disease of relatively long duration, and yet it distinctly shortens life expectancy by some thirty-five years for young males and an average of twelve years for the oldest age group.

DISCUSSION

The purpose of this analysis is to evaluate some of the problems of morbidity and mortality in multiple sclerosis. For the community the annual toll of deaths from the disease is relatively low. The main problem is medical care for a considerable number of persons with various degrees of disability. The three categories of disability represent progressively increased community costs, but neither relative nor absolute values can be assessed for each category from the data of the present study.

For the patient and his physician the eventual outcome of the disease is the paramount question. The disease invariably shortens the life of patients, more so in younger than in older people. Although death under present conditions occurs at an average of sixteen to twenty years after onset, the terminal event is preceded by a progressive disability and an eventual incapacitation of several years' duration.

Progress in the treatment and management of multiple sclerosis should be evidenced primarily in a lesser disability. It is true that insulin treatment of diabetes brought a remarkable increase in longevity of diabetic patients,[5, 6] but the gain is still more impressive when judged by the lesser disability and the fact that the majority of diabetic patients in modern times are active, working pro-

TABLE 2. *Median Expectancy for Work Production, Disabling Illness and Total Duration, by Age at Onset and Sex.*

AGE AT ONSET	MALE PATIENTS			NORMAL LIFE EXPECTANCY FOR MALES*	FEMALE PATIENTS			NORMAL LIFE EXPECTANCY FOR FEMALES*
	WORK EXPECTANCY	DEFECT AND DISABILITY EXPECTANCY	LIFE EXPECTANCY		WORK EXPECTANCY	DEFECT AND DISABILITY EXPECTANCY	LIFE EXPECTANCY	
yr.	yr.	yr.	yr.	yr.	yr.	yr.	yr.	yr.
10–24	<5	10.0	13.6	50.2	<5	13.9	21.8	54.2
25–34	<5	13.5	19.1	40.7	<5	14.9	19.5	44.5
35–44	<5	12.1	16.8	31.0	<5	13.4	18.7	34.9
45+	<5	6.7	9.0	22.5	<5	10.8	12.0	25.7
Averages	<5	11.1	14.2		<5	14.7	19.9	

*Computed from the life table of United States white population, 1939–1941.

ductive members of society. Severity of disease involves more than a fatal outcome. With the current emphasis on sickness rather than death as the primary concern of public health, there is need for precise definition of the effects of a disease, in terms of the three results it brings, which are disability, defect and death. The present paper attempts to measure some of these things, as they apply to multiple sclerosis, and from two aspects, that of the community and that of the patient and his physician.

Summary

Analysis of data from a field survey of multiple sclerosis in Boston and Brookline, 1939–1948, shows annual existing cases (prevalence) to be within four general categories, in which patients are described as working, ambulatory, bedridden or dying. The relative frequency among patients of a given year is, respectively, 35, 51, 21 and 3 per cent. Median life expectancy after onset of multiple sclerosis is fourteen years for males and twenty years for females. Males, on an average, reach the bedridden stage of disability about eleven years after onset, and females after fifteen years. Half the patients will discontinue work within five years of onset. These values are an indication of the cost to the patient.

More specific information is needed about the behavior of chronic disease generally, in population groups and about the community reaction in terms of nature and extent of disability, and of defect and death. The objective is an improved prevention. There is the added value that another means is provided for measuring progress in clinical management.

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RICKETTSIALPOX*

Report of a Serologically Proved Case Occurring in a Resident of Boston

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BOSTON

THE natural occurrence of rickettsialpox, a specific infectious disease caused by *Rickettsia akari*, has been observed only in New York City, where many cases have been reported since 1946.[1-5] A reservoir of the infectious agent exists in the common house mouse (*Mus musculus*) and transmission to man is believed to be effected by the mouse mite (*Allodermanyssus sanguineus.*)[6-8] The illness is marked by a primary cutaneous lesion, fever, systemic symptoms and a generalized exanthem.

The purpose of this paper is to report a case history clinically and serologically characteristic of rickettsialpox in a patient who had been continuously resident in Boston, Massachusetts, for five months prior to the illness. This case raises the possibility of the presence of the infectious reservoir in the Boston area, and indicates the desirability of watching for additional cases.

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Case Reports

E. K., a 56-year-old hat worker, had last visited New York City in 1947, and had resided continuously in Boston, Massachusetts, since September, 1949. She had never received inoculations of any rickettsial vaccine nor had she had any illness suggestive of a rickettsial disease. On the evening of January 30, 1950, a headache developed, and she noticed tender lymph nodes behind the right ear. The enlarged, tender lymph nodes persisted. Headache recurred on February 1, 1950, accompanied by malaise, chilly sensations and drowsiness. On the following morning these symptoms were much more pronounced; the temperature was 102°F. by mouth and she noted a spot on the face, as well as one on the right upper portion of the chest and two on the left forearm. That evening the patient was first seen by one of us (G.P.). The temperature was 101°F. by mouth, and the pulse rate 100. Several moderately enlarged, tender lymph nodes were palpable in the right posterior cervical chain, and one in the right supraclavicular region. The remainder of the physical examination was negative except for the skin. Approximately a dozen maculopapules were scattered over both arms, both legs and the trunk. Small gray-white, opaque vesicles were observed at the apex of two of these papules. There was a small papule on the right cheek.

On February 4 the symptoms were unchanged. The temperature was 99.2°F. by mouth (aspirin had been taken shortly before the visit), and the pulse rate was 100. The rash was now much more extensive. There were many maculopapules, diffusely scattered over the trunk and the extremities, sparing the palms and soles. No oral lesions were seen. The individual lesion was approximately 5 to 8 mm. in diameter, consisting of a small papule in the center of an erythematous base. At the apexes of a few of the papules, there were very small, gray-white vesicles. A careful

search was made at this time for a primary lesion. Two small, superficial, crusted lesions were found, one in the scalp behind the right ear and another below the right clavicle.

Drowsiness, headache, malaise and fever (maximum temperature of 101°F.) persisted, with a slight increase in the number of skin lesions until February 7, when definite subsidence of symptoms and moderate fading of the rash were noted. Steady improvement followed except for transient malaise with a temperature of 100°F. on February 9. The rash had almost entirely cleared by February 11, except for a tiny depressed scar at the site of the right infraclavicular lesion. No medication was taken during the illness other than a few aspirin tablets. The patient recovered completely and 2 weeks after the onset of the illness returned to her previous employment.

Examination of the blood on February 6 showed a white-cell count of 3900. On the following day a repetition of this count was 4800, with 48 per cent neutrophils, 46 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils.

Blood obtained on February 6 (the 8th day of disease) was inoculated into mice and cotton rats. No evidence of infection appeared. Passage of the livers and spleens of these animals to embryonated eggs gave no evidence of rickettsias.

Serum specimens taken during the acute illness and the convalescent period were studied for *Proteus OX* agglutinins and for complement-fixing antibodies to various rickettsial antigens.* The results of these tests are shown in Table 1. It is clear that they indicate a diagnostic rise in titer with the antigens of rickettsialpox and Rocky Mountain spotted fever. The usual control serums, both positive and negative, were included in the tests and assure the validity of these results. Repetition of these tests yielded identical results.

Two mice were trapped on March 2 at the patient's place of work. Examination for ectoparasites disclosed no mites.† Inoculation of the spleens of these animals into mice and cotton rats yielded no evidence of rickettsial infection. The patient was not aware of any similar illness among other persons at either her home or her place of work.

TABLE 1. *Tests on Serum Specimens.*

Date of Withdrawal of Blood	Day of Disease	Complement-Fixation Tests*					Weil–Felix* Test (Proteus)		
		Epidemic Typhus	Murine Typhus	Q Fever	Rocky Mountain Spotted Fever	Rickettsialpox	19	2	K
2/6/50	8	0	0	0	80	40	—	—	—
2/7/50	9	0	0	0	160	320	0	0	0
2/11/50	13	0	0	0	2560	2560	10	10	0
2/28/50†	30	—	—	—	—	—	0	—	—
3/22/50†	52	—	—	—	—	—	0	—	—
4/30/50	91	0	0	0	160	160	0	0	0

*The figures in these columns are the reciprocals of the final serum dilutions.

†These serums, as well as one obtained on February 19, were so highly anticomplementary as to preclude the possibility of performance of complement-fixation tests. We have no explanation for the anticomplementary properties of these serums. (These tests were performed by Miss Avis Ofstrock.)

Discussion

Rickettsialpox is usually heralded by a primary papular skin lesion, which undergoes vesiculation, followed by the formation of a black eschar, and heals with scarring.[9] It attains a diameter of 0.5 to 1.5 cm. and is usually distinctly larger than the lesions of the subsequent generalized eruption. The regional lymph nodes are usually enlarged and sometimes tender. Symptoms of rickettsialpox usually begin two to seven days after the appearance of the initial lesion. They include fever, the temperature ranging up to 104°F., chills or chilly sensations, headache, muscular pains and lassitude. The distinctive feature of the disease is the rash, which appears at any time from the first to the sixth day of fever. The lesions begin as erythematous maculopapules from 2 to 10 mm. in diameter. During the following two or three days a variable proportion of these develop at the apex of the papule, a small vesicle containing cloudy fluid. The vesicles usually give way to small crusts, which heal without scarring. The rash may be scanty or very extensive. The face, trunk and extremities are usually involved but in no characteristic order. Rarely, lesions occur on the palms and soles.[4] Lesions of the tongue, palate, buccal mucosa and pharynx are found in a minority of patients.[4] The fever, the systemic symptoms and the eruption may last from two to ten days. Clinical laboratory work is notable chiefly for a mild leukopenia.

The clinical features in the case presented above are in accord with the foregoing description of rickettsialpox: the duration of illness was eleven days; fever was present for approximately eight days; and the rash appeared on the fourth day of illness, was well marked for six days and gradually faded during the following four days. The appearance of the rash agreed closely with that described in the New York cases. An unequivocal primary lesion was not demonstrated. However, the enlarged, tender right posterior cervical and supraclavicular lymph nodes suggest either the scalp lesion or the infraclavicular lesion as possible primary sites. The infraclavicular site gains additional support from the residual scar noted after healing. No primary lesion was observed in 5 to 10 per cent of the previously reported cases.[3, 4]

The diagnosis of rickettsialpox is confirmed by the development in convalescence of a high titer of complement-fixing antibodies in tests with the antigens of *R. akari*.[10] The simultaneous occurrence of complement fixation with Rocky Mountain spotted fever antigen is a cross reaction that is regularly obtained in serums from cases of rickett-

*We are indebted to Dr. Herald R. Cox, Lederle Laboratories, for these diagnostic antigens.

†We are indebted to Dr. H. S. Fuller, Harvard School of Public Health, for this examination.

sialpox. The negative or very slightly positive Weil–Felix test with *Proteus OX-19* found in this patient is the rule in rickettsialpox. Rocky Mountain spotted fever, on the other hand, usually produces a distinctly elevated agglutinin titer for *Proteus OX-19* or *OX-2*. The inability to isolate a strain of *R. akari* by animal inoculation was perhaps due to the fact that blood was first taken rather late in the disease, when antibodies had already begun to appear.

The patient had frequently seen mice at her place of work, but no rickettsias could be found in the two mice thus far trapped.* A systematic search for rodents and arthropods infected with rickettsialpox in the patient's environment will be reported elsewhere.

Although the etiologic agent has not been isolated, the serologic data and clinical course warrant the assumption that the patient had rickettsialpox. If this is correct it is probable that she contracted the infection in Boston and therefore that the infected animal reservoir exists in Boston. An alternate but very unlikely mode of infection is that viable rickettsias were transported from New York, perhaps in the millinery material used in the patient's work.

Physicians in this region considering the diagnosis of rickettsialpox must differentiate chicken pox, smallpox, Rocky Mountain spotted fever and typhus fever (Brill's disease). Rickettsialpox is most commonly confused with chicken pox, but the differentiation is not difficult. The lesion of rickettsialpox is predominantly a maculopapule, often acuminate and containing a small vesicle within its apex. In chicken pox, the vesicle is the predominant feature and rests directly on the erythematous base. The exanthem of smallpox is not only different from that of rickettsialpox but also usually present on the palms and soles, where lesions of rickettsialpox are rarely seen. The absence of an initial lesion and the negative serologic reactions in these viral diseases complete the differentiation from rickettsialpox.

Rocky Mountain spotted fever and typhus usually produce a much more severe illness than rickettsialpox. The skin lesions may be macular or maculopapular, but vesiculation does not occur and a primary lesion is lacking. Rocky Mountain spotted fever and typhus fever regularly produce positive complement-fixation tests with the specific rickettsial antigens. Q fever is not accompanied by a cutaneous eruption.

R. akari have definitely been isolated from mice trapped in the patient's place of employment.[11]

Summary

A case of an illness diagnosed as rickettsialpox in a resident of Boston is described. The diagnosis was based on the occurrence of fever, a characteristic skin eruption and the appearance of complement-fixing antibodies to rickettsialpox and Rocky Mountain spotted fever antigens.

It is suggested that mice in this area may harbor the infectious agent.

Physicians should be alert for possible additional cases.

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MEDICAL PROGRESS

SYPHILIS*

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As this survey is being prepared, it is now approaching seven years since the first announcement of the treatment of syphilis with penicillin. Seldom in the history of medicine has there been a new treatment for any disease that was universally so dramatically effective and at once accepted. Penicillin is thus far standing the test of time, although some years must yet elapse before its ultimate value will be determined. Numerous improvements have come about in methods of administration, but the optimal dosage schedules are yet t be worked out. Despite these great strides in the treatm nt of syphilis, a great number of the basic problems regarding this disease remain unsolved.

PUBLIC HEALTH

With the passage of premarital-prenatal laws for Texas, thirty-seven states and the Territory of Hawaii have laws calling for premarital blood tests of both bride and groom.[1] Thirty-nine states, Hawaii and the Virgin Islands protect babies from syphilis by laws providing for a blood test of expectant mothers. There is lack of uniformity in the requirements of legislation enacted by the various states, but the basic intent is the same. It is difficult to understand why such measures are not universal. Most of these laws are not intended to prevent permanently the marriage of persons with syphilis, but are designed to control communicable syphilis until the disease has been rendered permanently noninfectious. Physicians called upon to fulfill the requirements of premarital laws should bear in mind that a negative blood reaction for syphilis does not by itself rule out the possibility of disease. A history and thorough physical examination are essential to detect the early seronegative stage of the disease. A single positive serologic test for syphilis, on the other hand, does not establish the diagnosis. It calls for more careful investigation and the possibility of a false-positive test must be borne in mind. It is generally considered that late syphilis of more than five years' duration cannot be transmitted and that it should not bar marriage. The same applies to congenital syphilis. If both parties to the intended marriage have syphilis, they obviously cannot infect each other, but the danger to progeny must be emphasized.

If one of the candidates for marriage has syphilis of less than five years' duration, the matter of adequate treatment must be considered. Hardly less than 2,500,000 units of penicillin can be considered adequate. If the clinical response and the serologic tests were satisfactory and all findings remained normal for a minimum of one year, the patient is usually considered past the likelihood of relapse. An examination of the spinal fluid should have been done, with normal findings. Some authorities prefer two years' observation after all tests have been negative. Regardless of the duration of the disease and the amount of treatment, however, it should be borne in mind that late visceral lesions, which carry a prognosis of shortened life expectancy or the possibility of involvement of the central nervous system, may bring disaster to the marriage. It should be obvious from these remarks that the requirements of any premarital law entail more than the simple performance of a serologic test for syphilis and the signing of a printed form.

Control Measures

The campaign against venereal disease has been aided by the use of radio programs for the past two years.[2] Dramatic, musical and documentary programs have been prepared in transcribed form in co-operation with Columbia University. They tell the venereal-disease story without offense and attempt to persuade those who suspect infection to seek diagnosis. Television programs were introduced at a later date. The United States Public Health Service is providing funds and assistance for these public-appeal campaigns. They have been found to be particularly effective when a thorough contact investigation is employed in the community. Co-operation between public-health departments and private physicians is imperative. It has been demonstrated that a follow-up service on the positive serologic reports obtained from specimens of patients receiving private care is of decided value.[3] When this maneuver is carried through so that contact-tracing service can be provided, many physicians will utilize the opportunity, and well trained personnel can be even more effective than the physician himself. It is accepted that the educational campaign carried on in the recent past has contributed greatly to solution of the problem

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of venereal-disease control, especially in certain segments of the population. Continued studies demonstrate, however, that well organized contact-tracing measures will still bring to light nearly as many cases of infectious syphilis as education.[4] It is also been shown, unfortunately, that multiple infections in the same person do not necessarily mean that the patient will always voluntarily seek medical care.[5] Contact investigation of syphilis should not be limited to infectious cases. All patients with newly diagnosed cases of syphilis are potential candidates for contact interviewing. Much latent disease can be uncovered by skillful interviewers with sufficient experience in contact tracing. Familial-contact investigation will lead to the discovery of congenital disease. Approximately 25 per cent of the syphilis now being diagnosed in clinics throughout the United States is discovered by means of contact investigation.[6]

One of the greatest difficulties with the old chemotherapy of syphilis was the problem of holding patients under regular treatment. With the shorter treatment schedules enabled by penicillin therapy and particularly since the advent of ambulatory penicillin therapy programs, the proportion of patients completing treatment has risen appreciably. Reports from clinics in all parts of the country indicate that 80 to 98 per cent of patients will complete ambulatory therapy schedules satisfactorily.[7-9] Obviously, the shorter the plan of treatment, the more co-operation can be obtained from the patient. Daily treatment schedules of ten to twenty days are in general quite satisfactorily completed. Older patients will usually co-operate the best. Differences in patients' education regarding the disease seem to be of paramount importance. Sufficient latitude of clinic hours to permit patients to carry on their usual work routine is also of value in case holding and regularity of clinic attendance.

The results of the application of psychiatric knowledge and technics to the field of venereal-disease control bring out an interesting approach to the treatment of promiscuity.[10] A comprehensive study was made of the personal and social factors affecting over 600 patients who voluntarily attended the psychiatric service of a large city clinic. Promiscuity appeared in most cases to be symptomatic behavior arising out of neurotic conflict, with such environmental factors as unsatisfactory living conditions and the absence of community ties. Lack of social responsibility and self-restraint was also a frequent finding. It seems obvious that psychiatric facilities in connection with a venereal-disease clinic can offer treatment that not only may result in reduction or elimination of promiscuity among patients who voluntarily utilize the service but also will promote mental hygiene as well as venereal-disease control.

Incidence of Syphilis

A chart of the reported civilian case rate of primary and secondary syphilis in the United States indicates that during the war years there was but little increase in the incidence of early syphilis.[11] Late in 1946 and early the next year there was a sharp rise, but a steady decline has ensued and by the end of 1949 early syphilis was being reported at the lowest rate of incidence since recording by stage began in 1941.[11, 12] These reported rates of incidence, however, reflect only the rate of discovery of the disease and not the actual numbers of cases in existence. Proof of this fact lies in the reported rates for discovery of early latent, late and late latent syphilis, which exceed the primary and secondary cases at least twofold. The obvious inference is that hardly half the actual early infections are being discovered, even though there is at present a slow but steady decrease in reporting of all stages of acquired syphilis. Such statistics emphasize the vital importance of continuing case-finding activity. There is no room for complacency even though the number of cases of early infection has been steadily decreasing in clinics, private practice and military services alike. There are areas in the United States that are not exposed to case-finding methods and in which syphilis goes undiscovered and untreated.[13] The United States Public Health Service is well aware of this situation, and the campaign will not be relaxed.

Syphilis mortality rates displayed a relatively stable incidence from about 1917 until 1935, when a distinct increase began.[14] In 1936 the nationwide venereal-disease-control program was initiated and between 1937 and 1946 there was approximately a 50 per cent decrease in the syphilis mortality rate per 100,000 population. This is an obvious illustration of the effectiveness of treatment when syphilis can be found and properly attended.

Experimental Studies

One of the most baffling problems in syphilis research has been the failure to grow pathogenic strains of *Treponema pallidum* on artificial culture mediums. Several nonpathogenic strains have been utilized for years in the study of animal syphilis, but none of these are the true pathogenic organisms of human syphilis. The chemical constitution of the treponeme is inadequately understood. It has long been thought that there may be transitional forms of the organism in which it assumes a spore-like resting stage and so forth. Peculiar formations of various sorts have been observed in cultured organisms when studied with phase microscopes and electron microscopes. The significance of these structures is not understood. Although syphilis can be successfully transferred to some laboratory animals, the differences in susceptibility or infectivity and the cause of the different reactions are

still unknown. If there are inhibitory factors operating in some animals that could be identified and isolated, the information might be of practical value when applied to the prevention of the disease in man. In rabbit syphilis, for example, the skin manifestations observed in human beings do not occur. Syphilitic lesions of the cardiovascular or central nervous system have not been observed in rabbits. As far as is known, syphilitic rabbits have not yet been kept throughout their entire life for studies at death to determine the extent of the pathologic process. Such an experiment is now being attempted.[15] This might throw some light on the inhibiting factors and the problem of tissue localization of syphilitic lesions. There are innumerable other unsolved biologic, laboratory and clinical problems in syphilis.[16] Little is known about natural or specific immunities in syphilis. False-positive serologic reactions, the time and method of fetal infection in congenital syphilis and the need for clearer differentiation between reinfection and relapse are a few examples.

It has been theorized that the affinity of *T. pallidum* for certain tissues may be in part related to the type of supporting ground substance and its permeability as affected by hyaluronidase (the so-called spreading factor).[17] It is not known whether the hyaluronidase is produced by the host or possibly by the spirochete itself. An attempt to induce the localization of *T. pallidum* in the aorta of the rabbit damaged by feeding of cholesterol is of interest.[18] Extensive atheromatosis developed in the aorta, aortic valves and coronary arteries. Some of the animals also developed xanthomatous deposits in the iris. When subsequently infected with *T. pallidum*, several of the latter animals developed an iritis in and about the xanthomatous lesions.

Immunity

The presence of an antibody in serums from syphilitic animals and human beings that immobilizes virulent *T. pallidum* in vitro has been demonstrated.[19] This antibody was found in serums from animals and human beings in various stages of syphilitic infection and could be differentiated from the Wassermann antibody (or reagin). Immobilizing activity was exhibited only in the presence of complement. The serums of over half of 20 cases of human primary syphilis showed some degree of immobilizing action, and a marked degree of immobilizing activity was exhibited in all serums from 20 cases of secondary syphilis. A similar number of serums from normal human beings were completely devoid of immobilizing activity. From absorption experiments it was concluded that the reagin played no role in immunity. It was believed that the immobilizing antibodies killed *T. pallidum* and must therefore be responsible for the immune state. Further studies of the same problem by other investigators have brought forth confirmatory results.[20] The treponemal immobilization test was used on the serums of 516 human patients. It was negative in all normal persons and in all with diseases other than syphilis. The immobilizing substance is nondialyzable, is associated with the globulin fractions of serum protein, requires complement for its demonstration and is relatively heat stable. The percentage of positive reactions to the immobilization test increases with the duration of the disease. This appears to be a useful tool in the research laboratory for the investigation of problems of immunity in syphilis and in the study of biologic false-positive reactions to serologic tests for syphilis, but the reliability and significance of the test will bear further evaluation. It is at least a step in the direction of clarifying the study of immunity in syphilis. It has been demonstrated earlier that there is an antibody response in rabbits to killed suspensions of pathogenic *T. pallidum* that has no effect on the immunity to syphilis.[21] This substance, the so-called reagin elaborated during syphilitic infection, merely happens to cross-react with the alcholic extracts of mammalian tissue, facilitating the Wassermann and flocculation phenomena. Animals injected with these suspensions of killed organisms will develop positive serologic reactions but cannot resist infection by living organisms.

A careful study of the rate of development and degree of acquired immunity in rabbit syphilis demonstrated that as the duration of the immunizing infection increased, there was a progressive increase in the number of *T. pallidum* required to produce symptomatic or asymptomatic reinfection after termination of the original infection by penicillin or arsenical therapy.[22] Although animal data cannot arbitrarily be transferred to human disease, it may be reasoned that at least some parallelism exists in human syphilis. If so, it might be assumed that human beings treated for primary syphilis would most often develop a symptomatic infection if re-exposed to syphilis, whereas patients treated during the secondary stage and subsequently re-exposed might develop symptomless reinfections in only a moderate number of cases. It might further be inferred that neither symptomatic nor asymptomatic reinfection would be of importance in those treated for late syphilis. At various times in the past, it has been suggested that syphilis should not be treated in its early stages for these very reasons. As far as I know, no one has yet had the temerity to practice this theory. The minimum number of spirochetes required to infect the rabbit is known, accurate means of measuring the inoculum are available, and the rate of multiplication of *T. pallidum* has been demonstrated, thus enabling rather accurate studies of the nature described.[22,23] Further study has demonstrated that the duration of acquired immunity in experimental syphilis in rabbits will persist for a considerable period. It

may be rather permanent, but the actual duration of this immunity has not yet been established. Rabbits cured by penicillin twelve weeks after infection could not be reinfected as long as forty-eight weeks after the treatment, even with inoculations of considerable size.[24] None of the animals showed any significant rise in serologic titer after reinoculation, even though some developed asymptomatic reinfections after overwhelming reinoculations.

Malaria

The first description of the pre-erythrocytic stage of mammalian malaria has been reported.[25-27] The developmental stages of pre-erythrocytic malarial parasites were demonstrated in the liver of a monkey, seven days after mosquito inoculation. The same finding was obtained by liver biopsy seven days after mosquito inoculation in a human being. The parasites of benign tertian malaria probably persist from one to three years in the tissues, giving rise at intervals to the relapses typical of this disease when transmitted by the mosquito. These tissue forms do not occur in malaria given by the intravenous inoculation of blood from a malarial donor, and relapses do not occur. This proved phase of naturally transmitted malaria should discourage further use of mosquitoes to induce therapeutic malaria. That procedure has been in relative disfavor for some time, but this discovery should terminate the practice in favor of intravenous inoculations from patient to patient in order that relapses may be avoided.

Experimental Therapy

An interesting study of the concentration of penicillin required to influence its rate of bactericidal action included effects on a cultured strain of *T. pallidum*.[28] It was observed that the concentration that killed the organisms at a maximal rate was two to twenty times the minimal effective concentration ("sensitivity" as ordinarily defined). Even a thirty-two-thousand-fold increase beyond this maximal effective concentration did not further increase the rate of bactericidal action of penicillin. A four-fold difference in concentration constituted the usual range of variation between the sensitivity threshold of the most susceptible and most resistant organisms in a given suspension. Differences in the susceptibility of bacterial strains to penicillin, in terms of the rate at which they can be killed, may well affect the length of time for which treatment must be continued to effect a cure. It was further observed that when the concentration of penicillin was increased beyond the optimal level, the rate at which organisms died in many strains was paradoxically reduced rather than increased. The maximal effect was thus obtainable only within a relatively narrow optimal zone. This would seemingly shed some light on the studies of time-dose relations of syphilis therapy and suggest correlation with the fact that tremendous doses of penicillin in a very short time have not been too effective.

A comparison of the therapeutic efficacy of penicillin G in experimental syphilis produced by five different strains of *T. pallidum* showed a considerable variation.[29] Neither the length of time that a strain had been maintained by animal passage in rabbits nor the number of passages appeared to be the significant factor responsible for variation. The strain requiring a maximum amount of penicillin needed five times as much penicillin per kilogram of body weight as the least resistant strain. Three of the strains had been isolated in recent years from penile chancres by the intratesticular inoculation of rabbits. The wide variation in the amount of penicillin required to cure the infected rabbits might have some bearing on the fact that this drug will not cure a greater percentage of patients with syphilis.

It has been possible to produce asymptomatic neurosyphilis in the white mouse, and this fact was utilized to assay the therapeutic value of penicillin, Mapharsen and Tryparsamide.[30] It was concluded that penicillin was the only drug showing therapeutic activity. Maximum tolerated doses of Tryparsamide and Mapharsen had no appreciable therapeutic value, and exceeding these doses would be fruitless because of toxic effects.

New Drugs

After the remarkable efficacy of penicillin in the treatment of syphilis, it was only to be expected that newer antibiotics should be studied for their possible value in the treatment of this disease.

Aureomycin has received the most attention. It has been found that aureomycin is readily absorbed into the general circulation and is excreted rather slowly.[31] No cumulative effect appears to follow multiple doses provided there is no impairment of renal function. After its absorption, aureomycin diffuses readily into the cerebrospinal fluid in amounts that may be considered therapeutically effective. It also diffuses through the placenta and is available in the fetal circulation. When therapeutically effective amounts of aureomycin are present in the serum, it may also be demonstrated in the pleural fluid, hepatic system, kidney, spleen and lung. A number of reports have appeared describing the oral administration of aureomycin in the experimental treatment of human syphilis.[32-37] There is general agreement that aureomycin appears to have antispirochetal activity when administered by the oral route. Early syphilis, late cutaneous syphilis and neurosyphilis have all been studied to a limited extent with this treatment, and results are encouraging. The advantage of oral medication is obvious in spite of the hazards of self-medication. The demonstration of aureomycin in the spinal fluid after oral administration may create a special

place for the use of this drug in neurosyphilis. Penicillin-sensitive patients would obviously provide an ideal situation for the administration of aureomycin if this drug withstands more extensive investigation satisfactorily. It is unfortunate that practically 100 per cent of patients receiving the required dosage of aureomycin have developed mild to moderate gastrointestinal disturbances. Other side-effects of the drug are gradually coming to light. A great deal more study will be required to decide the final value of aureomycin in syphilotherapy. The correct dose and proper time intervals are yet to be determined. It may be that this agent will prove to be of greatest value as an adjuvant to penicillin therapy. Obviously, aureomycin must be categorically regarded as a purely experimental antisyphilitic drug for the present. It is also being used in rabbit syphilis, but has a relatively high degree of toxicity for these animals.

The antitreponemal effect of chloramphenicol (Chloromycetin) has also received attention, but there is not general agreement regarding its value.[38-40] Bacitracin is likewise being investigated and may prove valuable in the treatment of syphilis.[41] Both these substances can be discussed only on experimental grounds at present.

Serologic Problems

There has been no significant progress in clarification of the serodiagnosis of syphilis within the past year or two. With the advent of cardiolipin somewhat earlier there was hope that this new phospholipin component of antigen would lead to the simplification of the serodiagnosis of syphilis. Cardiolipin antigens have been adapted to various technics that formerly employed lipoidol antigens, and various new technical methods have been devised. The actual number of testing procedures has increased, but as yet it has not been conclusively demonstrated that the use of cardiolipin in serologic tests for syphilis has increased the specificity of the tests or simplified the situation in any way. Cardiolipin is a purified chemical extract of beef heart that, when properly combined with lecithin and cholesterol, forms a serologic antigen.[42, 43] These components can be chemically standardized, and a serologic assay can be conducted to determine the relation of the antigenic properties. A properly prepared cardiolipin antigen is believed to be more specific than the older and more crude lipoidol antigens. Under the authority of the Coordinating Committee on Laboratory Methods of the American Public Health Association, a committee has been formed for the purpose of formulating, evaluating and establishing reference-standard serologic methods for the serodiagnosis of syphilis. The development and adoption of the standard antigens and tests for syphilis by the state laboratories would not preclude the use of diagnostic procedures that are now employed. In various laboratories a standardized level of sensitivity, however, might produce sufficient information in terms of syphilis and yet be relatively free from biologic false-positive reactions. It is believed that further study will increase the specificity of cardiolipin antigen, and some less specific technics could be discarded. An extremely high index of sensitivity and specificity has been obtained by employing the cardiolipin-lecithin indicator in the Hinton test.[44] Over 16,000 serologic tests were performed in this study. A similar report based on the results of over 24,000 blood samples, which were subjected to more than 80,000 tests, disclosed confirmatory findings.[45] Eight technics of testing were employed, three of which utilized the cardiolipin antigen. The relative stability and reproducibility of cardiolipin with somewhat higher sensitivity and greater specificity led these workers to recommend universal tests based on cardiolipin. Examples of new technics employing the cardiolipin antigen are a macroflocculation test for syphilis in blood serums and a macroflocculation spinal-fluid test for syphilis.[46, 47] It is to be hoped that the aforementioned committee will be able to agree on a standard test for universal reference and perhaps discourage the multiplication of technics. The burden of interpretation of any serologic tests for syphilis still rests on the shoulders of the clinician and must be correlated with the clinical findings.

The cardiolipin-lecithin antigen is also employed in the titred (quantitative) serologic tests for syphilis. These procedures reflect the amount of reagin present in the blood serum and are especially valuable in watching the response to treatment, detecting treatment failure, indicating impending relapse, giving evidence of reinfection, differentiating congenital syphilis of the newborn from a temporary reagin titer carried over from fetal circulation and sometimes in diagnosing a false-positive serologic reaction. Quantitative serologic tests are also in need of standardization in both technic and method of reporting. The dilutions may represent an arithmetic series or a geometric series. These recordings may also be expressed in units.[48]

False-Positive Tests

It has been stated that at least 58 different factors can invoke false-positive serologic responses for syphilis.[49] This discussion is a most lucid consideration of the problem of "biologic false" reactions to serologic tests for syphilis. It derives from a study of the records of 68 patients who had been under extended observation for the interpretation of a positive serologic reaction for syphilis in whom a diagnosis of nonspecific positive reaction had been considered. Twenty-three of these cases were finally eliminated because an ultimate diagnosis of syphilis was made. The complicated and puzzling character of the biologic false or non-

specific positive reaction was emphasized. It appears to be a part of a general infection reaction mechanism shared by many diseases and forms of injury, more developed in some persons than in others. Febrile states, especially those due to infections, virus diseases, foreign-protein inoculations and certain specific diseases such as leprosy, malaria and infectious mononucleosis are particularly apt to bring out biologic false-positive reactions. There is reason to suspect that a seronegative status in a well treated syphilitic person may be converted into a temporary seropositive state by some of the agencies that can produce a biologic false-positive state. Syphilitic patients approaching a serologic cure may be maintained for some time in a state of low-titer fluctuation by a tendency toward the biologic false-positive reaction. The proportion of false-positive reactions in all tests and in serologic surveys probably does not exceed 1 in 700 cases. A much higher percentage of nonspecific positive reactions may be found in occasional groups of routine positive reactions. Every test in which the reaction is positive should be repeated, and the patient should be checked for the more common possible causes of biologic false-positive reactions. The decision to treat must be withheld until the situation has been evaluated and every possibility has been thoroughly investigated. The pregnant woman approaching term might be an exception. The temptation to use a large amount of penicillin as short-cut to a decision is becoming more common and should be seriously resisted. It is not a light decision to fasten a diagnosis of syphilis on any patient. In the absence of other evidence, the serologic pattern should be studied over as long a time as possible and by as many means as are available.

Long lists of circumstances in which biologic false-positive reactions may be encountered are cited by other writers, and the more rare false-positive serologic reactions in the spinal fluid have been reported in brain tumor, encephalitis, malaria and mumps.[50] A group of 104 volunteers inoculated with malaria by mosquito bite developed temporary false-positive serologic tests for syphilis in 72 per cent of the total number.[51] False-positive reactions following vaccination against smallpox have been reported to occur in from 9 to 17 per cent in two groups of known nonsyphilitic patients.[52, 53] A serologic survey of 692 battle casualties revealed positive serologic tests for syphilis in 34.5 per cent of the cases.[54] The highest incidence was observed in the more severe traumatic cases. Only 1 patient was ultimately thought to have syphilis.

Early Syphilis

For all practical purposes penicillin has come into dominance over the entire field of syphilotherapeutic agents. Nevertheless, there is far from agreement regarding the most efficient schedule of penicillin treatment. The United States Public Health Service has surveyed 45 penicillin schedules used in treatment of secondary syphilis.[55] In only about a third of these methods was it possible to obtain 80 per cent satisfactory results. Some of the more efficient dosage schedules will be delineated in succeeding paragraphs. It is of interest to note that the first 4 patients treated with penicillin have been observed for six years.[56] The members of the group were young males with seropositive primary syphilis. They received 25,000 units of an amorphous penicillin preparation at four-hour intervals for a total of forty-eight injections. This routine provided 1,200,000 units of the antibiotic and a treatment period of eight days. The clinical and serologic responses were satisfactory and have remained so. Spinal-fluid examinations from each patient gave no evidence of abnormal changes. This pilot study of the use of penicillin in human syphilis has brought about a complete realignment of the entire structure of syphilotherapy.

Diagnosis

A revision of *The Diagnosis of Syphilis by the General Practitioner*, by Dr. Joseph Earle Moore, special consultant to the Public Health Service, has been published as Supplement 23 to the *Journal of Venereal Disease Information*.[57] The clinical diagnosis of syphilis is covered in detail. The important role that the practicing physician plays in the control of syphilis is emphasized. A completely new section on the interpretation of laboratory tests for syphilis has been added. The various technics used in blood and spinal-fluid tests are discussed. The interpretation of blood serologic tests and of spinal-fluid tests is described and discussed in relation to the biology of syphilitic infection. This little booklet should be of value to anyone dealing with syphilis and in particular to the general practitioner. Supplement 23 can be purchased from the Superintendent of Documents, Government Printing Office, Washington 25, D.C., for twenty-five cents per copy. The Massachusetts Department of Public Health has revised the standards for the diagnosis, treatment and follow-up study of patients with gonorrhea and syphilis who are seen in the State co-operating venereal-disease clinics.[58]

Symptomless infection with syphilis provides a diagnostic problem for the physician and one that is often most difficult to explain to the patient. An excellent example of the occurence of symptomless infections was observed during the German occupation of Brussels.[59] All registered prostitutes were kept under rigid supervision and underwent a complete medical examination twice a week, with serologic tests for syphilis every two months. In a period of five and a half years 170 of these women who had been repeatedly examined and repeatedly had had negative blood tests, developed positive serologic tests for syphilis without any clinical

manifestations. This group comprised more than 50 per cent of the women who developed syphilis while under observation.

With the widespread use of penicillin, the diagnostic difficulties presented by patients hospitalized for other conditions and found to have positive serologic tests for syphilis after penicillin therapy can be a source of considerable confusion. This is particularly true if the patient has an infection known to be capable of producing a biologic false-positive reaction.[60] If there is no clinical evidence of syphilis and no history suggesting it is obtainable, the situation is further complicated. Even small amounts of penicillin may have a decided effect on the level of syphilitic reagin so that titred serologic tests will not immediately clarify the diagnostic difficulty. Spinal-fluid examinations are imperative in these situations. A period of three months or longer of careful observation may be required to clarify the diagnostic dilemma in these cases. The withholding of penicillin, unless urgently needed, would lessen the diagnostic hazard.

Penicillin Blood Levels

There are accepted minimal therapeutic concentrations of penicillin in the blood that vary for different organisms. These blood levels of penicillin do not indicate the amount present in the various body tissues at the sites of infection. The penicillin blood concentration that has become generally accepted as a minimal effective therapeutic level in syphilotherapy is 0.03 units per cubic centimeter. There are also maximal blood levels, which are the amounts thought to produce the greatest destruction of organisms in the shortest period. Repository types of penicillin preparations have been further improved so that minimal therapeutic concentrations will remain in the blood for periods upwards of twenty-four hours. The concentration of penicillin in the tissues is probably at a maximal effective concentration for only a portion of that time, but it is thought that the tissue-defense mechanism can operate more effectively even though tissue penicillin concentrations are not constantly maintained at maximal levels. Experimental studies with penicillin water-in-oil emulsion, penicillin epinephrine in oil and procaine penicillin in oil with aluminum monostearate have been demonstrated to show effective serum concentrations of penicillin for protracted periods and to produce satisfactory clinical and serologic response.[61-64] The procaine penicillin with aluminum monostearate seems to have been the most satisfactory. The oral administration of penicillin salts will also produce therapeutically effective blood levels of the drug, but they are not as high and are maintained for shorter periods.[64, 65]

It has been known for some time that the administration of caronamide reduces the rate of excretion of penicillin and thereby results in higher blood levels. Continued study of these drugs has been confirmatory with both injection and oral administration of penicillin.[66-69] The serum penicillin concentration attained with the use of penicillin in addition to caronamide was from two to four times as great as that obtained with the use of penicillin alone. No renal or hepatic impairment has been observed in these studies, but it is believed that there has not been sufficient experience with caronamide to state that it is entirely free of chronic toxicity. There appears to be disagreement whether penicillin traverses the blood-brain barrier under normal or abnormal conditions. The concurrent administration of penicillin and caronamide has shown therapeutically effective levels of penicillin in the spinal fluid.[70] When penicillin was administered intravenously, it was more effective in producing a therapeutic level in the spinal fluid.[71]

"Abortive" Treatment

A most effective preventive or "abortive" approach to the problem of those exposed to known infectious syphilis has been described.[72, 73] A prophylactic treatment was administered to 256 persons who had been in contact with infectious syphilis but who had not shown evidence of having acquired the disease. A combined treatment consisting of penicillin and bismuth injections given in immediate succession and followed by intravenous arsenoxide was administered at the same visit. Patients exposed more than two months prior to the interview were not included. During the latter part of the study, the arsenoxide injection was omitted. Early syphilis subsequently appeared in 13 persons, and retreatment with the abortive procedure was successful in 10 of these. Eight of the 13 in this group had definitely been re-exposed to infectious disease, and the evidence suggested that this may have been true of the other 5 in whom the disease developed. Eight more who received abortive treatments were protected a second time by retreatment following a new exposure to infectious syphilis. The effectiveness of the prophylactic treatment was substantiated by the fact that early syphilis appeared in 62.1 per cent of a control series of 161 persons exposed to infectious syphilis, but not given the abortive treatment. Such measures should not only help reduce the spread of the disease to others but also decrease the incidence of reinfection of the original person who was the source of infection and who would have meanwhile completed therapy ("ping-pong" syphilis). The abortive treatment consisted finally of 900,000 units of penicillin calcium in oil and wax in one buttock and 3 cc. of bismuth ethyl camphorate (120 mg. of elemental bismuth) in the other buttock. A confirmatory report on a small group of patients with slightly less prophylactic therapy has appeared.[74] Although this procedure has as yet

enjoyed relatively limited study, it seems to hold considerable promise.

Penicillin Dosage

The mere fact that so many plans of penicillin therapy have been under study is obvious evidence that the optimal treatment schedule has not been established. It has been stated by numerous writers that penicillin is superior to all other forms of antisyphilitic therapy, both in safety and in therapeutic effectiveness, but contrary opinions regarding the efficacy of penicillin are not difficult to find. Some careful students of the therapy of syphilis still believe that penicillin alone is somewhat inferior in therapeutic activity to properly administered metallic chemotherapy, provided the latter is carried out completely.[75] It is uniformly agreed, however, that penicillin is remarkably low in toxicity and that its ease of administration is a great convenience to patients and physicians alike. Crystalline penicillin G was quickly recognized as being superior to amorphous penicillin, especially when the latter contained a significant content of penicillin K. Therapeutic results with penicillin in oil and beeswax ("POB") may or may not seem superior to crystalline penicillin in aqueous solutions, depending upon the therapy schedule. The still newer procaine penicillin is now being even more highly regarded. Numerous possible alterations of time-dose relation intended to increase blood and tissue concentrations and the concomitant use of other spirocheticides are constantly being studied.

It is impracticable to report all the treatment plans appearing in the literature, but a representative few are cited to indicate the trend in therapeutic procedures. When groups of patients are subdivided into the various stages of early syphilis, the seronegative primary group invariably is found to have the lowest failure rate by any treatment plan. Progressive increases in frequency of relapse are seen as the disease progresses through seropositive primary, secondary and early latent stages. For practical purposes, it is thought better to consider so-called cumulative failure rates in attempting to assay various treatment schedules; these cumulative failure rates include all the substages of early syphilis, and the failure rates as cited below are cumulative rates. There are also slight variations in results according to race and sex, but in general these are not of great importance.[76] Higher failure rates among Negroes are thought to be due mainly to the difficulty in separating relapses from reinfections, and the latter seemed definitely more common among the colored race.

The early dosage plan including 1,200,000 units of penicillin administered during a period of seven and a half days was quickly found to be inadequate, resulting in approximately 30 per cent failures.[77] Several groups of patients treated with 2,400,000 units of penicillin in seven and a half days were found to have a cumulative failure between 20 and 30 per cent.[78-80] Doubling the amount of penicillin to 4,800,000 units or carrying it on to 9,000,000 or 10,000,000 units seemed to make no remarkable difference since the cumulative failure rates still vary between 20 and 30 per cent.[81-86] In several of these groups, however, increasing the time factor from seven and a half to fifteen or sixteen days appeared to have a favorable influence. Another treatment plan suggests 300,000 units of repository penicillin daily for twenty days.[87] Larger amounts are advocated in case of relapse.

The mechanism of action of penicillin has been studied by many investigators, and it is believed that the drug exerts its effectiveness in preventing the growth and multiplication of susceptible organisms. Under ordinary conditions, penicillin is most effective against actively growing and dividing strains. Thus, the more active the growth of the strain, the more prompt and effective the reaction of penicillin. Dormant or inactive organisms may not be destroyed by penicillin and may resume growth after penicillin administration has been discontinued. It is important to know, therefore, whether *T. pallidum* has a dormant phase longer than the average duration of penicillin schedules currently employed.[88] From information now available, penicillin must be active within the body for a minimum of several days to bring about the cure of any appreciable percentage of cases of early human syphilis.[89] Since the average cumulative failure rate for the eight-day schedules have been at best about 20 per cent, there is some opinion that the optimal period of treatment should be about fifteen days.[90, 91] This would include a daily dosage of 300,000 units of the repository types of penicillin, of which procaine penicillin G appears to be the dominant agent. Patients given rapid treatment for syphilis must be observed at frequent intervals for at least two years, preferably with quantitative serologic tests. About 75 per cent of successfully treated patients become seronegative within six months after penicillin therapy for early syphilis. The other 25 per cent may have low reagin titers for varying periods after six months, but they do not require retreatment unless the titers show evidence of relapse or reinfection. The evaluation of rapid treatment of early syphilis would be much more exact if it was possible to differentiate accurately between relapses and reinfections. With the aforementioned fifteen-day schedule, the optimal amount of penicillin appears to lie somewhere between 2,500,000 and 9,000,000 units.

Semiweekly penicillin treatments have been investigated to some extent and several groups of patients have been treated twice weekly for three to eight weeks with substantial doses of repository penicillin. Preliminary studies indicate that results may be just as satisfactory as the more concentrated fifteen-day schedules.[82, 90, 92, 93] It has

been demonstrated that a single injection of 1,200,000 units of procaine penicillin will provide a therapeutically effective blood level of the drug for approximately a week, and this has led to the investigation of single-treatment schedules, two-day plans, three-day schemes and weekly treatment programs.[94-96] There appears to be some promise in these studies, but they must be regarded as strictly investigative procedures and are cited here only as a matter of interest.

To summarize current thought as briefly as possible, the penicillin treatment of early syphilis appears to be most desirably planned for a fifteen-day course utilizing from 300,000 to 600,000 units of procaine penicillin daily.

Combination Therapy

Arsenical agents and bismuth are steadily dropping into disuse for the treatment of syphilis. There is an opinion in some quarters that combining penicillin with metallic chemotherapeutic agents is of value, but arsenic in particular is generally believed to add too little of value to offset its greater hazard of serious reactions.[97, 98] Combination therapy, nevertheless, has numerous advocates, who advise various schedules of concurrent penicillin and metal therapy.[97-102] Several of these reports include relatively high percentages of success, and there are some large series of patients with lower failure rates than those obtained with penicillin alone. One authority presents seven different "acceptable" schedules of treatment that include penicillin alone and assorted combined treatment programs.[98] Considerable work has been done on combination therapy in rabbits, and some additive value appears to be demonstrable.[103] Nevertheless, in human syphilis there are a certain number of conflicting data, and the status of combination therapy seems to be somewhat in doubt.

Fever therapy has been used to a lesser extent in early syphilis than in neurosyphilis, and the results have generally been less satisfactory than with other methods. Considerable work has been done, however, on combining fever with penicillin and fever with penicillin and chemotherapeutic agents.[104] Results were relatively good in this report, in which all three forms of treatment were used concurrently during a period of thirty hours. This highly specialized technic is not applicable to general use, and the hazards of fever in addition to arsenotherapy do not justify the addition of these agents to penicillin alone when the latter has proved so outstandingly successful.

Reinfection and Relapse

The difficulty of distinguishing between reinfection and relapse has proved so difficult since the advent of rapidly effective treatment programs that most of the reported failure rates have included all dubious cases among relapses. Criteria for reinfection should include stable seronegativity over a protracted period, negative cerebrospinal fluid, a new primary lesion at a different site from the previous chancre, proof of contact with infectious syphilis and adequacy of treatment of the preceding infection. In one group of 140 recurrent infections, 70 per cent were considered to be reinfections.[105] A similar series of patients was found to consist of approximately 60 per cent reinfections.[106] Nearly all the relapses in the latter group were found to occur within the first year after treatment, and the authors went so far as to say that, for practical purposes of differentiation, a patient presenting infectious syphilis more than a year after penicillin therapy for early syphilis should be regarded as having a reinfection rather than an infectious relapse. This is perhaps true, but every effort should be made to clarify the situation.

An analysis has been reported of the relation of early clinical failure to serologic response within the first post-treatment year in penicillin-treated early syphilis, based on data from 16,150 cases selected from records of thirty-eight clinics in a nationwide penicillin study.[107] The data revealed a high degree of correlation between serologic response during the first year after treatment and the probability of clinical failure. In other words, when the serologic response was favorable, the cumulative failure rate was low.

It is known that after penicillin treatment of early syphilis some patients will maintain a low titer of serologic positivity for several months and that retreatment need not be considered. If, however, the serologic test persists in high titer for six months, it seems advisable to administer retreatment regardless of whether clinical relapse has appeared. It is obvious that a patient with unmistakable serologic relapse should always be retreated as soon as the fact is established. Rapidly repeated serologic checks should be consistently confirmatory, with a repeatedly high titer.

A study has appeared on the spinal-fluid findings in patients who relapse after penicillin therapy for early syphilis.[108] Prior to the original treatment, 12.9 per cent exhibited abnormal spinal fluids; this is about the expected ratio. A second spinal-fluid examination was done at the time of retreatment. Among 45 whose spinal fluids had originally been abnormal, there were 62 per cent with abnormalities after relapse. In the larger group of 304 whose spinal fluids had originally been entirely normal, 14.5 per cent displayed abnormal spinal-fluid findings at the time of retreatment. This suggests that the risk of invasion of the nervous system is approximately the same during relapse as during the original infection with syphilis.

Reinfection following late syphilis has been an exceedingly rare occurrence, even though the disease has been adequately treated. This is usually explained on the basis of acquired immunity re-

tained after the treatment for late syphilis. Two cases of symptomatic reinfection occurring in patients previously treated for cardiovascular syphilis and, in 1 case, simultaneous neurosyphilis, have been reported.[109] It may be assumed that this phenomenon is due to cure of the original infection and the gradual disappearance of whatever immunity it may have engendered. It is not believed that the human race has much, if any, natural immunity to syphilis, although the fact is known that many persons exposed to infectious syphilis apparently escape infection. Asymptomatic reinfections may occur in some cases of late syphilis and be undetected. It is thought that asymptomatic reinfections may represent a partial immunity sufficient to destroy the majority of spirochetes so that no local lesion develops, but that this partial immunity is insufficient to destroy all the organisms.[110] The extent to which changes in immunity may influence failure or relapse rates in clinical syphilis has so far not been ascertained, but it might be expected that a previous infection with syphilis would in some respects modify the effects of a subsequent exposure to the disease.

Transfusion Syphilis

It has become rather generally accepted that the refrigeration technics employed in blood banks have practically done away with the possibility of transfusion syphilis. Exceptions may occur when emergency transfusions are performed in the absence of access to a blood bank, when there is no time to wait for serologic tests of donors or when a donor is employed who happens to be in a seronegative phase of early syphilis. It has been shown that patients given transfusions of plasma from donors with a positive serologic reaction for syphilis will acquire a positive serologic reaction for syphilis.[111] The initial titer of the acquired reaction represents the dilution in the recipient's blood volume of the reagin contained in the injected plasma. This acquired positive serologic reaction for syphilis will revert to negative within a few weeks. Blood donors with syphilis should therefore be acceptable for use in any blood bank with a plasma program, provided the material has been frozen, dried from the frozen state or stored at least four days in the refrigerator. This is comforting in view of the fact that virulent spirochetes were demonstrated in the blood of three fourths of a group of patients with secondary syphilis, when inoculated into rabbits.[112] Spinal-fluid specimens from the same patients were transferred to rabbits, resulting in 20 per cent positive inoculations. All patients whose spinal fluid produced an infection also had virulent organisms in the blood. The risk of transfusion syphilis, in the absence of a blood bank, may be reduced by the use of blood or serum treated with sodium citrate and preserved by refrigeration at 4°C. for four days.[113, 114]

(To be concluded)

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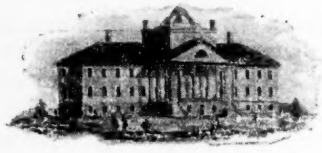
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36491

PRESENTATION OF CASE

First admission. A seventy-two-year-old ex-bartender entered the hospital complaining of dysphagia.

Nine months prior to admission the patient first noted increasing fatigue and anorexia and began to have occasional episodes of vomiting and burning epigastric pain that occurred one or two hours after eating. The pain was relieved by alkali but aggravated by food. Four months before admission the pain and vomiting became more frequent, occurring at intervals of one to three days. Two months before admission the patient developed dysphagia and an aversion to meat. He had lost 10 pounds in weight in the year prior to admission. Hematemesis and change in bowel habits were denied. There was a questionable history of tarry stools four years previously.

Forty years before entry he had a questionable episode of tuberculosis treated by two months of bed rest. Thirty-two years before admission he acquired a penile chancre. Fifteen years later he developed a pustular eruption of the forehead and back, which he sometimes ascribed to an infected grease burn and at other times stated had been diagnosed as "tuberculosis of the skin." Four years before admission he had received at another hospital a course of 40 bismuth and 22 Mapharsen injections, following which the spinal-fluid Wassermann test was negative but the blood remained positive. In the ten years prior to admission he had made numerous visits to another hospital for treatment of dyspnea, orthopnea, palpitation and persistent precordial pain, and had been on digitalis most of this time, with some relief of symptoms. A palpable liver was noted three years before admission, and there had been one attack of severe pruritus shortly before admission. The patient stated that he rarely coughed but produced large quantities of white mucoid sputum, which never contained blood. He had had nocturia (two times) for six months before admission but denied other urinary symptoms. There was occasional mild constipation, which responded to milk of magnesia. Ten years before admission he had an operation for a strangulated right inguinal hernia at another hospital. The hernia recurred and was controlled by a truss.

He had been separated from his wife and living in rooming houses for some thirty years. His alcoholic intake was said to have been 4 glasses of ale per day. The family history was noncontributory.

On physical examination the skin was sallow and had atrophic scarring over the forehead and left lumbar region. Early lenticular opacities did not prevent visualization of narrow, tortuous retinal arteries. The chest was hyperresonant throughout and clear to auscultation. The heart sounds were of good quality. There was normal sinus rhythm with frequent premature beats. A Grade II systolic murmur was heard over the precordium loudest at the apex and was transmitted into the axilla. There was a large, smooth, tender, right-upper-quadrant mass extending down as far as the umbilicus that was believed to be the liver. A few soft inguinal lymph nodes were palpable. An easily reducible direct inguinal hernia was demonstrated on the right. Rectal examination revealed a moderately enlarged prostate. Neurologic examination was negative.

The temperature, pulse and respirations were normal. The blood pressure was 170 systolic, 98 diastolic.

The urine had a specific gravity of 1.014, and gave a +++ test for albumin; the sediment contained 5 to 10 white cells per high-power field. Examination of the blood disclosed a hemoglobin of 12 gm. and a white-cell count of 6700, with 74 per cent neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 2 per cent basophils. Three stools obtained shortly after admission were guaiac negative. Gastric analysis revealed free hydrochloric acid. The corrected sedimentation rate was 1.4 mm. per minute. The bromsulfalein test showed 36 per cent retention of the dye. The total protein was 6.96 gm., with an albumin-globulin ratio of 1.3. Thymol turbidity was 1.5 units, the thymol-flocculation test was negative, the cephalin-flocculation test was negative in twenty-four and forty-eight hours, the van den Bergh reaction was less than 0.2 mg. per 100 cc. direct, 0.4 mg. per 100 cc. total, and the prothrombin time was 13 seconds (normal, 15 seconds). The cholesterol was 84 mg., the alkaline phosphatase 3.4 units, and the nonprotein nitrogen 82 mg. per 100 cc. Two urea-clearance tests were 10 per cent and 13 per cent of normal. Phenolsulfonphthalein excretion was 17 per cent in two hours. A Congo-red test showed 75 per cent retention in the serum. A urine concentration test showed a maximum specific gravity of 1.010. The venous pressure was equivalent to 140 mm. of water. The circulation time from arm to tongue as measured by Decholin was 25 seconds. An electrocardiogram disclosed auricular fibrillation at a rate of 85 and was believed to be consistent with left ventricular strain and hypertrophy. A gastrointestinal series showed coarse mucosal folds suggestive of chronic gastritis. The duodenal cap was scarred, but no ulcer crater could be demonstrated. The heart was moderately enlarged on fluoroscopy, particularly on the left. The aorta was calcified, and the lung fields clear. There was some calcification in the right renal area and around the celiac axis. A barium-enema examination was negative. Repeated blood Hinton, Kahn and Wassermann tests were positive.

The patient was placed on a low-salt diet, digitalis, 0.1 gm. every other day, ammonium chloride, 6 gm. per day, and ferrous sulfate, 0.78 gm. per day. He did well until the sixth hospital day, when he suddenly vomited about 2000 cc. of guaiac-positive material. Over the next twelve hours he received two subcutaneous injections of 0.065 gm. of phenobarbital and 0.0004 gm. of atropine each, after which he went into coma followed by drowsiness that lasted for three days. During this period the nonprotein nitrogen rose to 156 mg. per 100 cc. Three stools obtained during the remainder of the hospital course were all guaiac positive. Since the patient was believed to be unduly sensitive to digitalis, this drug was discontinued. The nonprotein nitrogen gradually fell to 75 mg. per 100 cc.; there was no further vomiting, and he was subjectively much improved. The dysphagia cleared without specific therapy. During the third and last week of the hospital stay he received a course of intramuscular injections of penicillin as antisyphilitic therapy, without untoward reaction.

Final admission (ten months later). Three months after discharge, the patient, who was being followed in the Medical Clinic, was found to have a blood pressure of 210 systolic, 130 diastolic, auricular fibrillation at a rate of 150 and increased cardiomegaly. The lungs were clear, there was no ankle edema and the only complaint was pruritus. Six months after discharge he returned to the clinic complaining of severe dyspnea and periumbilical pain. The liver at this time descended to the iliac crest. The nonprotein nitrogen was 7.6 mg. per 100 cc., and an x-ray film of the chest showed mild bilateral pleural effusion and prominent vascular markings consistent with pulmonary edema. This improved briefly following routine cardiac therapy in a nursing home. Over the next few months, however, he went steadily downhill, with progressive anorexia and respiratory embarrassment. The liver gradually decreased in size until it was palpable only two fingerbreadths below the costal margin.

The day prior to admission he came to the Emergency Ward, where the apical rate was noted to be 130 and irregular. An electrocardiogram showed bundle-branch block and an abnormal rhythm, which could not be interpreted. He was started on quinidine, 0.2 gm. every four hours, but after a total of 0.8 gm. was found unresponsive, with no detectable pulse or respiration. He revived following administration of Coramine and was admitted to the hospital.

Physical examination revealed a surprisingly alert, cheerful man, with distended neck veins. Dullness and decreased breath sounds were noted at the left base. The heart showed no change. A sharp, smooth, tender liver edge was felt two fingerbreadths below the costal margin, and there was bilateral costovertebral-angle tenderness.

The temperature and respirations were normal; the pulse was 120 and irregular. The blood pressure was 150 systolic, 90 diastolic.

The urine had a specific gravity of 1.012 and gave a ++ test for albumin, and the sediment contained 20 white cells per high-power field. Examination of the blood revealed a hemoglobin of 13.8 gm. and a white-cell count of 9300. A stool was guaiac negative. The sodium was 132.9 milliequiv., the potassium 4.9 milliequiv., the chloride 104 milliequiv., and the carbon dioxide 24.8 milliequiv. per liter, and the nonprotein nitrogen 88 mg., and the calcium 8.3 mg. per 100 cc. Several electrocardiograms showed auricular fibrillation and bundle-branch block.

During the first two days in the hospital the patient had explosive diarrhea. A left thoracentesis performed on the second day yielded 650 cc. of straw-colored fluid with a specific gravity of 1.010. He received 1 cc. of Mercuhydrin on the third hospital day and 0.1 mg. of digitoxin on the seventh day. He went progressively downhill, with weakness, anorexia and erratic rhythms, and died quietly on the eighth hospital day.

Differential Diagnosis

Dr. John B. Stanbury*: May I see the x-ray films? I am particularly interested in the calcification around the kidneys and in the celiac axis, and also in whether or not he had an enlarged spleen.

Dr. Joseph Hanelin: The chest films taken at the time of the first admission demonstrate emphysematous lungs but otherwise clear lung parenchyma and an obviously enlarged heart, chiefly in the region of the left ventricle. The aorta is tortuous and shows calcification within its wall. There is no indication of an aneurysm. About five months later the chest films reveal definite evidence of congestive failure, with some fluid at either base, more marked on the left side. Six weeks following that there has been clearing of the congestive changes in the lung although some fluid is still present. At the time of the last admission ten months later considerable fluid is present in the left pleural space.

An upper gastrointestinal series and films of the colon, which were taken at the time of the first admission, show some changes in the stomach consistent with gastritis. The duodenal bulb is irregular, but there is no crater. There does appear to be a duodenal diverticulum, and the liver is somewhat enlarged. A right inguinal hernia is in evidence by virtue of the small bowel that has entered it. Calcification overlies the kidneys and appears to represent renal-artery calcification on the right side. On the left side the calcification over the renal area is not in the usual distribution of the renal vessels although it may be partially within the renal-artery tree. The kidneys are small. There is no splenic enlargement.

Dr. Stanbury: Thank you very much.

This is a long and complicated protocol and the only way I can attack the problem is to discuss it from several different points of view. First I wish to consider the heart. The patient's illness apparently began about ten years before admission with dyspnea, orthopnea, palpitation and precordial pain, and for the next ten years he was treated with digitalis presumably for congestive heart failure, which became progressively worse. When he came to the hospital ten months before the final admission his physicians found a Grade II systolic murmur with an enlarged liver, a venous pressure equivalent to 140 mm. of water, a circulation time of 25 seconds and an elevated blood pressure of 170 systolic, 98 diastolic. An electrocardiogram showed left ventricular strain and auricular fibrillation, and the x-ray films demonstrated an enlarged heart. These symptoms cleared to a degree, and in three weeks he was sent home. In the intervening ten months there was a progressive increase in the dyspnea and in the size of the heart. The blood pressure at one time was 210 systolic, 130 diastolic, and on one x-ray film bilateral pleural fluid was described. At the time of the final admission distended neck veins were present. The blood pressure was still elevated, but only to 150 systolic, 90 diastolic. Auricular fibrillation and bundle-branch block were still present. A left thoracentesis was done the next day, with the removal of 650 cc. of fluid. I think the only conclusion I can draw from this is that the patient had chronic congestive heart failure. I am a little puzzled by the left-sided chest fluid. The x-ray films several months before the final admission had shown bilateral pleural fluid. Whenever one finds left-sided pleural fluid he is not accustomed to ascribe it to heart failure unless he can show obliteration of the pleural space on the right. It is conceivable, I suppose, that the patient had a pulmonary infarct although he had no clear history for it. The pleural fluid of a pulmonary infarct need not be bloody. I think I cannot make the diagnosis of pulmonary infarct on the present evidence.

What was the basis of the congestive heart failure? I think I can rule out the possibility of syphilitic aortitis and failure on that basis. I think I can also rule out rheumatic heart disease despite the fact that he had a Grade II systolic murmur. This leaves me with hypertension as the sufficient cause. One wonders whether the hypertension was primary or whether it derived from renal disease. I anticipate, then, that hypertensive and arteriosclerotic heart disease was found.

Whether the hypertension arose from primary renal disease is the next consideration. Throughout the hospital course an elevated nonprotein nitrogen, — at one time as high as 156 mg. per 100 cc., — a urea clearance of 10 to 13 per cent, a phenolsulfonphthalein test of 17 per cent, a constant albuminuria and fixed urinary specific gravities were found. This renal picture is perfectly consistent with the end stage of glomerulonephritis, with nephrosclerosis, with pyelonephritis or even conceivably with amyloid disease. I do not know how to choose among the various possibilities. Certainly, there may well have been an element of pyelonephritis. At one time bilateral costovertebral-angle tenderness and 20 white cells per high-power field in the sediment were found. I think there was an element of pyelonephritis but I am more inclined to count the renal disease as being due to progressive nephrosclerosis as part and parcel of the congestive heart failure and progressive arteriosclerosis.

*Assistant physician, Massachusetts General Hospital.

The third problem relates to the group of symptoms — anorexia, vomiting, epigastric burning, dysphagia and aversion to meat — that brought him into the hospital originally. When he was examined free hydrochloric acid was found in the stomach, and on x-ray examination he had coarse mucosal folds. I am not sure to what the dysphagia was due. It cleared up rapidly after admission. One wonders about the diet; he had lived alone for thirty years and, being a bartender, probably did not eat very well. I suppose, since the dysphagia and the mild anemia cleared on proper diet, that this was a Plummer–Vinson syndrome, and I shall let it go at that. He never had any dysphagia during the final ten months. However, the x-ray films showed thickened mucosal folds and some scarring of the duodenum. While in the hospital he vomited 2 liters of guaiac-positive material and the stools became guaiac positive. I wonder if the ammonium chloride he had been receiving contributed to gastric irritation and atony and whether this, with the hypertrophic gastritis, caused some bleeding and vomiting.

There are a number of other points that I should like to mention briefly. Throughout this history there was a suggestion of sensitivity to drugs: digitalis, atropine and quinidine. He took digitalis for ten years. When he came to the hospital he was given ammonium chloride and iron, and then he vomited. Then I read that it was thought that he was sensitive to digitalis and consequently the drug was stopped. On subsequent occasions he came in with a rapid heart rate and auricular fibrillation. One wonders if he really was sensitive to digitalis or whether the upset stomach was part and parcel of the uremia and gastritis. Later, this patient with evidence of liver impairment and uremia was given two doses of 0.4 mg. each of atropine, and 0.065 gm. (1 gr.) each of phenobarbital on two occasions. He promptly went to sleep and was drowsy for the next three days. This may have represented an idiosyncrasy, but I think he was probably unable to get rid of the phenobarbital, which is excreted partly by the kidneys and partly by the liver. Atropine is excreted almost entirely by the kidneys, but I doubt if it contributed to the stupor in this dosage.

The third and most dramatic episode occurred when he was given quinidine to a total of 0.8 gm. in twelve hours for a cardiac arrhythmia; he was found unresponsive and without respirations and pulse. With aminophylline he seemed to come around all right. I do not think this represented necessarily an idiosyncrasy to quinidine. On every other occasion when his cardiac rhythm was determined, he had auricular fibrillation. I wonder whether at this time too he was fibrillating, and the quinidine slowed down the auricular circus so that the ventricle was then able to respond to more of the auricular beats and he then developed essentially an auricular flutter at a very rapid rate, and cerebral anoxia. That is one possible explanation for the collapse.

The evidence suggesting impairment of the liver is the bromsulfalein test showing 36 per cent retention and the fact that the liver was enlarged, at one time to the iliac crest and at others two or three fingerbreadths. With the history of a mild alcoholic intake and of being a bartender, one wonders about cirrhosis. This seems unlikely because on physical examination there was nothing but the large liver to suggest it and all the other tests were normal. The spleen was normal in size, and I assume that no varices were found when the gastrointestinal series was done. Also I doubt very much if syphilis played any part in this man's illness. The skin lesions may have represented some old tertiary syphilids, but I do not believe that syphilis accounted for the enlarged liver.

There are several things that I cannot explain. I cannot explain why he had an elevated sedimentation rate of 1.4 mm. per minute. I think one often finds old healed myocardial infarcts in patients who have had hypertension for long periods. It is conceivable that he had a relatively symptomless infarction and that the sedimentation rate represented a reaction to it.

I do not know how to explain the periumbilical pain noted on several occasions in the Out Patient Department, and the explosive diarrhea at the time of the final admission. I cannot explain the calcification about the celiac axis and in the kidney, but I suppose it should be attributed to calcification of vessels.

I should like to make diagnoses of hypertensive and arteriosclerotic heart disease, nephrosclerosis and superimposed pyelonephritis, chronic hypertrophic gastritis and benign prostatic hypertrophy.

Dr. Jacob Lerman: I believe a well digitalized patient who has a diuresis from ammonium chloride and mercurials and has a reaction, has ordinary digitalis intoxication and not hypersensitivity. The digitalis bodies are concentrated in the body and are not excreted as rapidly as the fluid.

The other point I should like to discuss is the liver, which was very large on the first admission. At one time in the course of the Out Patient Department workup, the liver was said to have reached the iliac crest and then to have shrunk rapidly down to two fingerbreadths in spite of the fact that the patient was getting worse. Why should the liver get smaller? One must consider the possibility of some necrotizing process in the liver such as subacute yellow atrophy without jaundice.

Dr. Allen G. Brailey: Does anyone know whether the patient may have been giving himself alkali and whether that may have contributed to the kidney failure by any chance?

DR. HUGH CHAPLIN, JR.: I do not recall specifically, but certainly it was not brought out in the routine history.

DR. RICHARD E. GOLDSMITH: There are two questions I should like to ask. One is whether Dr. Stanbury thought the 2000 cc. of vomitus a little unusual without evidence of pyloric obstruction, and the other is whether or not the four months of frequent vomiting associated with epigastric pain is a common concomitant of so-called deficiency gastritis.

DR. STANBURY: I would rather attribute it to gastritis, which I assume he had. I am assured by physicians here that 2000 cc. of vomitus is not an uncommon finding in chronic gastritis. I think the three months of vomiting probably would go along with gastritis.

DR. CHAPLIN: The 2000 cc. of vomitus can be explained by the fact that the patient, in preparation for a phenolsulfonphthalein test, had been given a large water intake immediately prior to the episode of vomiting.

Our opinion on seeing him on admission was that he had considerable congestion. We thought that the diagnoses Dr. Stanbury has made were probably correct but that there might also have been something else going on because we could not quite put it all together.

A PHYSICIAN: How can you rule out syphilis? He had had a chancre forty years previously.

DR. STANBURY: I do not rule out syphilis. I am sure he had it, but I do not think it contributed to the final disease. He was treated with penicillin for some time before he entered this hospital.

CLINICAL DIAGNOSIS

Hypertensive cardiovascular disease with uremia.

DR. STANBURY'S DIAGNOSES

Hypertensive and arteriosclerotic heart disease.
Nephrosclerosis, with superimposed pyelonephritis.
Chronic hypertrophic gastritis.
Benign prostatic hypertrophy.

ANATOMICAL DIAGNOSES

Miliary tuberculosis.
Nephrosclerosis and pyelonephritis.
Hypertensive heart disease, mild.
Cirrhosis, old, alcoholic.
Gastritis.
Duodenal ulcer, healed.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy was also quite complicated. The heart was enlarged, weighing about 400 gm., and showed a hypertrophy of the left ventricle that was consistent with mild hypertensive heart disease. The coronary arteries seemed to be in quite good shape — just a mild sclerosis. The aorta showed a very severe degree of sclerosis, and all the calcification on the abdominal films was due to calcification in the splenic and renal arteries and the other branches of the aorta. The inferior mesenteric artery was reduced to half the usual size by severe calcification. The main renal arteries, although sclerotic, were open, but as one approached the hili of the kidneys, the lumens were almost completely obliterated. This decreased blood supply apparently accounted for the small atrophic scarred kidneys, which together weighed 150 gm. Microscopically, they showed severe arterial disease with luminal narrowing but also evidence of a chronic infection. The tubules were atrophic and contained so-called colloid casts and in many areas small foci of calcium deposits, which perhaps was a result of pyelonephritis or a calcinosis due to the long-standing renal insufficiency. There was a good deal of calcification in the tubules of the kidneys and even around the tubules. I believe that the renal picture was a combination of a severe nephrosclerosis resulting partly from obliteration of the main supply of blood to the kidneys and a pyelonephritis.

The liver was pushed down a bit. It was not really enlarged, weighing only 1250 gm., but showed a definite cirrhosis. It was a burned-out cirrhosis, probably of the alcoholic type.

The cause of the increased sedimentation rate and most of the findings that were not readily explained was a miliary tuberculosis, which this man had in practically every organ of the body. It is surprising that he had no fever. This was not just an old tuberculosis but acute disease with caseation and Langhans giant cells throughout both lungs and pleura. The terminal ileum had a large tuberculous ulceration, which accounted for the explosive diarrhea and pain and also for the guaiac-positive stool. The whole small bowel was very hemorrhagic, but there was only one large ulcer in the terminal ileum. The duodenum did have evidence of a healed ulcer, and there was a great deal of inflammation of the stomach — a true gastritis. In addition to the cirrhosis we were able to find a few tubercles scattered throughout the liver. There was not much tuberculosis in the kidneys, but in the pelvis of the kidney we discovered a few tubercles. We also found tubercles in the adrenals, spleen and bone marrow.

DR. STANBURY: That is depressing, Dr. Castleman. I would not know how to make that diagnosis even in retrospect.

CASE 36492

PRESENTATION OF CASE

An eighty-seven-year-old woman was admitted to the hospital because of lower abdominal pain of approximately twelve hours' duration.

When she awoke on the morning of the day of admission the patient began to have a dull aching

pain in the lower abdomen, most marked in the right lower quadrant. She had orange juice for breakfast but had nothing but water until admission. Anorexia and nausea developed in the afternoon. She had one normal bowel movement. By evening the pain in the lower abdomen had increased in severity, and she was brought to the hospital. The pain was never crampy, and there had been no previous attacks.

She had been severely ill with peritonitis when she was about nineteen years old but recalled no details of the illness. There was no history of subsequent abdominal complaints. She had been seen at this hospital a number of times. The first admission was eleven years previously, when amputation of the four smaller toes of the left foot was performed because of long-standing fungous infection that failed to respond to conservative therapy. Nine years before entry x-ray films revealed scoliosis, kyphosis and Paget's disease of the skull and spine. One year later a plaster-of-Paris jacket was made to relieve pain associated with the Paget's disease. She was next seen three years before admission because of a small mass in the right breast. Study of her general condition showed little change. An intraductal fibroadenoma was removed, and she apparently got along well until the present episode.

She had always been constipated, requiring laxatives. The menopause had occurred at fifty years of age, and there had been no bleeding since.

Physical examination revealed an anxious and sick, elderly woman with arthritic joints and sclerotic vessels. The heart was enlarged, with a Grade III systolic apical murmur. The lower abdomen was full and moderately tympanitic. Peristalsis was diminished, although present and essentially normal in pitch. There was tenderness in the right lower quadrant generally, and there was definite rebound tenderness in the right abdomen on release of pressure in the left. On rectal examination there was mild tenderness in the right vault. No masses were felt, although the entire cul-de-sac was full. What was taken to be the uterus was tiny and lay in the midpelvis. The ovaries were not felt.

The temperature was 99.6°F., the pulse 94 and irregular, and the respirations 20. The blood pressure was 200 systolic, 110 diastolic.

The urine had a specific gravity of 1.020 and contained no albumin or sugar. The sediment contained 10 to 15 white cells per high-power field. The white-cell count was 12,000.

Approximately one hour after admission an operation was performed.

Differential Diagnosis

Dr. Irad B. Hardy*: This is the problem of an elderly woman with an acute process in the abdomen. The chest and urinary tract were ruled out as the source of symptoms. A good deal of the past history was probably noncontributory to the present illness. It is interesting that the patient remembered having peritonitis sixty-eight years before admission, in 1882. That was about four years before Dr. Fitz's† historic paper on appendicitis. I believe she had an acute abdominal illness from which she recovered without an operation. She was then well except for chronic constipation, which had not changed in recent years until the present illness.

Twelve hours before entry there was a dull, gradually increasing steady pain in the lower abdomen associated with some anorexia and some nausea but no vomiting or other abdominal symptoms. On physical examination she had an elevated blood pressure that was probably consistent with her age and an irregular pulse that may have been due to extrasystoles or auricular fibrillation. There was some fullness of the abdomen but no distention. Peristalsis was present and essentially normal although slightly diminished, presumably being associated with some acute process in the abdomen and peritoneal irritation. There was also definite tenderness localized chiefly in the right lower quadrant and rebound tenderness referred to the same area. The rectal examination was chiefly confirmatory of the presence of some process in the right lower quadrant. The laboratory findings showed a slight elevation in the white-cell count.

In a woman of this age, there are a few main possibilities that I have to consider. In the first place, I shall consider some form of vascular disturbance. She had hypertension; it is very possible that she had a dissecting aneurysm of a slowly leaking nature that had pushed down the right iliac vessels and produced symptoms in that region, but I do not believe the rest of the findings fit in with that. She was in the age group certainly for mesenteric thrombosis, but she did not appear to be as acutely ill as she would have been with a mesenteric arterial thrombosis. The history was too short for her to have entered the hospital and to have been operated upon for a venous thrombosis. That is an insidious process, and some time elapses before the surgeon can make up his mind to operate. She could have had a small mesenteric embolus arising from a sclerotic plaque in the aorta, but the onset of the pain was too slow for this sort of process.

Probably the most common cause of acute abdominal symptoms in elderly patients is intestinal obstruction. The patient had some abdominal disease years before and might have had mechanical obstruction due to a band or adhesion. A volvulus of the cecum, sigmoid or even the small bowel is a possibility. The picture was certainly not typical of either of these conditions. The pain had been gradually increasing and had been steady. There

*Assistant in surgery, Massachusetts General Hospital.

†Fitz, R. H. Perforating inflammation of vermiform appendix: with special reference to its diagnosis and treatment. *Am. J. M. Sc.* 69:321, 1886.

was no colic and no vomiting. Physical examination showed no distention, and peristalsis was essentially normal. There was no evidence that she had an external hernia, such as a femoral hernia that was strangulated. The chance of some sort of internal herniation is remote — the symptoms would have been similar to those of other types of acute obstruction.

If she had a malignant tumor hidden away, one would think she might have had something prior to the acute symptoms to suggest gradual encroachment on the lumen. I do not believe she showed the picture of a cancer that had perforated. Again, I do not think she was as acutely ill as she would have been with such a lesion. I also think that this was not the picture of a perforated ulcer or gastric cancer. Acute shock and pain was not present although in elderly patients some of these symptoms may be much diminished.

Among the inflammatory group of diseases, I believe that cholecystitis — both acute unperforated and perforated gall-bladder conditions — is as common as any condition in this group of patients, and some gall bladders may be down in the right lower quadrant. Although cholecystitis is common, I do not believe she had it.

Diverticulitis, of course, is the other common inflammatory condition in this age group. The constipation she had had for years would favor diverticulosis. There are usually some prodromes that last for several days or weeks before a very severe diverticulitis develops. Of course, the symptoms were entirely or mostly in the right lower quadrant; the symptoms of diverticulitis are more often on the left side of the abdomen.

What I believe is the diagnosis that best fits this patient is acute appendicitis, although not typical. It would be interesting to know whether or not the original illness years before entry had been appendicitis with perforation and recovery. Whether or not it was, I think the present episode of abdominal pain localizing in the right lower quadrant, with signs of peritoneal irritation without obstruction, fits in best with this diagnosis. My impression is that the surgeons probably had the same thing in mind when they operated on her upon admission to the hospital.

DR. BENJAMIN CASTLEMAN: The preoperative diagnosis was acute appendicitis. Dr. Donaldson, would you tell us what was found at operation?

CLINICAL DIAGNOSIS

Acute appendicitis.

DR. HARDY'S DIAGNOSIS

Acute appendicitis.

ANATOMICAL DIAGNOSIS

Small-bowel obstruction due to adhesive band, secondary to spontaneous appendectomy years previously.

PATHOLOGICAL DISCUSSION

DR. GORDON A. DONALDSON: I shall have to confess to my preoperative diagnosis, because it is down in black and white. Our explanation for operating on this elderly woman so suddenly was that we were rather certain that the diagnosis was acute appendicitis. It also should be said that she came into the hospital in the middle of the night, was very sick and obviously had disease in the right lower quadrant; so that we thought it best to go ahead. At operation the pathology presented itself immediately. It was only then that her son, a physician, who was standing nearby, recalled that he had been told that his mother had been acutely ill as a girl. As we mobilized the cecum more and more trying to find the appendix, the cause of her acute episode became clear. We could not find the appendix. There was, however, a small nubbin where the white taenia came together that was obviously the base of the appendix. The cecum was fixed by an adhesion with a solitary band lying across the terminal ileum that had caused a subtotal obstruction to the ileum.

In reconstructing the events that undoubtedly took place in this case, I think it is fair to say that more than sixty-eight years previously this patient had spontaneously carried out an appendectomy on herself. Such cases have been reported in the literature, and occasionally a segment of the disintegrated appendix goes on to form a mucous cyst. At any rate, in this case the appendix had completely disintegrated, and there was nothing left other than a few millimeters of its base. The adhesive band and the rather thickened veil that held the cecum were the traces of a previous, rather diffuse inflammatory process.

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THINGS TO COME

A LITTLE crystal-gazing on the part of the editors of the *Journal*, made reasonably accurate as the result of months of patient toil and reams of persuasive correspondence, renders it possible for them to venture a prediction of things to come. This glimpse into the future reveals in fact a considerable mass of information about events already in the past that is being regrouped and prepared for early publication.

In respect to such a prediction even Lewis Carroll would have been excited at the prospect of looking forward to looking backward, particularly if it consisted in the anticipation of a series of some twenty-four Medical Progress reports by approximately two dozen authors, on fifty fruitful years in their particular branches of medicine. For this is what the *Journal* has in preparation.

This new and special series of progress reports, the publication of which will begin early in January and will proceed in orderly but inflexible fashion until its conclusion, is intended to summarize the important events of a half century in various ramifications of the healing art, no attempt being made to cover them all. The series will present rather the major advances on a single broad front, separated into two divisions. The first of these will consider medicine as a science, the second, medicine as a social instrument. The authors are eminent in their fields.

The most confidential advice that the circulation manager has to offer, in view of a possible paper shortage, is for those unhappy few nonsubscribers to the *Journal* to enter their subscriptions now, in order that they may enjoy uninterrupted readership of the entire series.

But more anon.

BE YE TRANSFORMED

The Lancet, over a considerable period of time published regularly a series of articles under the general heading "Disabilities." Representing the personal experiences of patients in overcoming the handicaps imposed by a variety of chronic diseases or other crippling conditions, the majority of these articles were of practical as well as inspirational value to others who might be suffering from the same or similar limitations.

A striking example of "him that overcometh" is Hamilton Cameron, of New York, a doctor of philosophy as well as of medicine, who has related the story of his own recovery from the right-sided hemiplegia and complete aphasia that had resulted from a cerebral embolism.*

Dr. Cameron has given much of his life to inspirational guidance and encouragement through his writings and broadcasting. The founder and secretary of National Shut-In Week, he is also the founder of The Benevians, a nonprofit membership organization chartered in New York to carry on a program of "practical fellowship," with regular radio broadcasts. In 1943 a sudden stroke left him immovable, unable to speak or to write.

*Cameron, H. I came back after a stroke. *Journal of Living*, July, 1949.

When discouragement gave way to a determination that he would utilize fully every step that nature might provide in the way of recovery, Dr. Cameron inaugurated his own painful program of rehabilitation. Gradually he relearned walking, after a year words came to his mouth, and in his second year he held a pencil, although it was another year before he could write out his thoughts. After six years no apparent physical trace of the illness remained.

As part of Dr. Cameron's return to usefulness, he devised a simple system of communication by hand-signs, in which only one hand need be used in making simple wishes known. A chart demonstrating this method, which can be employed in cases in which the teaching of a complicated hand-sign language is impractical, has been printed and is freely available to physicians on application to Dr. Cameron at 601 West 110th Street, New York.

Dr. Cameron believes — and who can deny him? — that the reason for much of his recovery can be summed up in an excerpt from *Romans* **12**:2: *--be ye transformed by the renewing of your mind.*

PROBLEM OF MULTIPLE SCLEROSIS

THE great strides made in the treatment of acute diseases have now extended the frontiers of medical investigation to the territory of chronic illnesses, which are just beginning to be explored by modern clinical methods. Multiple sclerosis is the most important example of chronic diseases of the nervous system. Elsewhere in this issue of the *Journal*, Ipsen clearly delineates the magnitude of the problem that this disease presents in terms of human lives and productivity, thereby helping to outline a blueprint for adequate facilities for the care and study of those afflicted.

He reports an incidence rate of 50.8 per 100,000 population. Of these patients approximately a quarter (12.5 per 100,000) are working full time, about half (26 per 100,000) are ambulatory but partially disabled, and approximately another quarter (12.3 per 100,000) are seriously ill — that is, bedridden or dying.

If these incidence rates are expressed in terms of the population of Massachusetts, it appears that at any one time approximately 2200 persons afflicted with this disease are living in the Commonwealth. Expressed in terms of needs for medical services and care, the 550 who are still working require at least semiannual checkups, the 1100 who are ambulatory but sick require office or outpatient facilities, and the 550 who are bedridden require hospital accommodations. These bedridden patients at present are scattered through a few chronic hospitals, some private homes and a great number of nursing homes, most of them woefully inadequate for the proper care of such patients. Thus, not only does great human suffering go inadequately alleviated, but great opportunity for scientific study is lost as well. Modern methods of clinical investigation have not yet been brought to bear upon this problem on a sufficiently large scale.

The second set of data, which are of fundamental importance in Dr. Ipsen's study, are those concerning the natural rate of progression of the disease. His excellent tables supply an adequate yardstick for measurement and comparison of future progress in treatment and clinical management. This important section of the article is also of great value in tempering judgment regarding the prognosis of the illness. Although the seriousness of the prognosis of the natural course of the illness is statistically beyond any doubt, one should be exceedingly careful in prognosis. It is very instructive to note that 30 per cent of male patients are still working five years after onset of illness, 23 per cent ten years after onset, and 8 per cent fifteen years after onset, 3 per cent at the end of twenty years, and three per cent after twenty-five years. For females the figures for retained working capacity are 34 per cent at the end of five years, 25 per cent at the end of ten years, 11 per cent at the end of fifteen years, 9 per cent after twenty years, 8 per cent after twenty-five years, 5 per cent after thirty years and 4 per cent after thirty-five years. The preponderance of females among the group with retained working capacity is obviously due to the fact that housewives are included in the working group, but it is significant that 3 per cent of the males are still working at a time that may be presumed to be the normal retirement age of the group.

Apart from its statistical incidence, the very fact that such a happy course of events is at all possible in such a severe illness is a heartening one, since it proves that the disease is not necessarily incurable or uncontrollable. Many important leads for treatment of an illness have been derived from observations of natural recovery or control. Study of such fortunate patients contrasted with those who do poorly may be fruitful in producing a significant clue to pathogenesis and therapy.

The author's finding of the prevalence of the disease in females is significant in that it confirms the figures of other surveys both in Europe and in this country.

There is a definite need for a long-term longitudinal study of patients — what means there may be for predicting and preventing exacerbations, and to study possible chains of events that may produce either a favorable or an unfavorable course.

Through the foresight of the National Multiple Sclerosis Society a research clinic has been established at the Boston State Hospital, and has been actively functioning for two and a half years. This clinic enjoys the sponsorship of the newly established Massachusetts Chapter of the National Multiple Sclerosis Society. Its clinic population at present is 210, with 183 on the waiting list, making a total of 393. The incidence rate of this disease certainly indicates that a still larger case material is available that is in need of co-ordinated observation and study from many points of view and by many methods, in order to provide the valid observations necessary for a fruitful conceptual scheme that may give a clue to the solution of this problem.

RICKETTSIALPOX IN BOSTON

In 1946 an outbreak of a febrile illness of several days' duration occurred in the borough of Queens, New York City, among residents of a large housing unit. A distinguishing feature of the disease was a maculopapular rash with tiny central vesicles. There were no deaths. The disease was thoroughly investigated by the New York Health Department and the United States Public Health Service with the co-operation of a pest-control operator[1] and New York physicians.[2] A micro-organism was obtained from the blood of patients, from the tissues of house mice trapped in the building and from mites found in association with the mice and their nests. The micro-organism was named *Rickettsia akari*, and the disease was called rickettsialpox.

Since 1946 several hundred cases of rickettsialpox have been recorded in four of the five boroughs of New York City, but the disease has not been reported elsewhere. The reservoir is the house mouse, *Mus musculus*, and the vector is the mite, *Allodermanyssus sanguineus*; these species are known to be widely distributed, and physicians have, of course, been expecting the appearance of rickettsialpox in areas other than New York City. By virtue of its immunologic properties, *R. akari* is related to the micro-organisms that cause Rocky Mountain spotted fever. Like the other members of this group, rickettsialpox does not spread from man to man. The human disease is an accidental occurrence unrelated to the maintenance of the infection in nature.

In this issue of the *Journal* the first case of rickettsialpox is reported outside the New York area by Pike, Cohen and Murray. The patient, a resident of Boston, had not left that city for several months prior to her illness, which occurred in January, 1950. The clinical course and the serologic data are consistent with the diagnosis of rickettsialpox. This case history prompted the Massachusetts Department of Public Health and the Department of Microbiology of the Harvard School of Public Health to search for *R. akari* in mice or mites in the building in which the patient was employed in downtown Boston. Although relatively few mice and mites were found, several trials for isolation of rickettsias were made; a micro-organism very similar to the MK strain of rickettsialpox from New York City was obtained from the tissues of 2 mice of 22 examined.[3]

The paucity of mites and mice in this building and the small proportion of positive mice found there represented conditions unlike those under which the first outbreak of rickettsialpox was observed in New York. A second case in the Boston area has recently been recognized[4] and further sporadic cases in Boston are to be anticipated, but

the appearance of these 2 cases does not necessarily imply that an outbreak is in immediate prospect.

References

1. Roueché, B. Alerting of Mr. Pomerantz. *New Yorker*, August 30, 1947. P. 28.
2. Huebner, R. J. Rickettsialpox and Q fever. *Bact. Rev.* **14**:245-248, 1950.
3. Fuller, H. S., Murray, E. S., Ayres, J. B., and Snyder, J. C. Unpublished data.
4. Franklin, J., and Wasserman, E. Rickettsialpox: first reported case in Massachusetts. *New Eng. J. Med.* (in press).

Dr. John Hastings, of San Francisco, charged Mayor Bigelow, of Sacramento, $4000 for attending to the wounds he received in the riot. Dr. Bowie charged $500 for consulting!

Boston M. & S. J., *December 4, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

Mendelsohn — Louis Mendelsohn, M.D., of Saratoga, California, died on November 12. He was in his seventy-first year.

Dr. Mendelsohn received his degree from Harvard Medical School in 1904. He was a fellow of the American Medical Association.

His widow, a daughter, a brother and three sisters survive.

CORRESPONDENCE

CLARIFICATION OF PREMARITAL LAW

To the Editor: In the September 14 issue of the *Journal* Dr. Allen S. Johnson, of Springfield, Massachusetts, called attention to some provisions of the recently enacted premarital law that he thought needed amplification. The Massachusetts Department of Public Health is happy to utilize the medium of the *Journal* to clarify the points raised by Dr. Johnson, realizing that other physicians may have had the same questions.

Basically, Dr. Johnson asks how thorough the examination for syphilis should be, and he states that, "if the genitals and the urethral mucosa of the male show no syphilitic lesions, and if his serologic test is negative, the physician will probably exonerate him with reasonable confidence." Most physicians will agree to this statement provided there is also no history of recent exposure.

However, Dr. Johnson continues, the examination of the female presents a different problem in view of the possible presence of seronegative primary syphilis. Should the examining physician perform a pelvic examination on all female applicants? The answer to this is left to the physician's judgment, for the individual case will show clearly whether or not a pelvic examination is indicated.

Physicians know that every patient infected with syphilis must have been exposed to another person with the same disease. Approximately 95 per cent or more of such exposures have been sexual in character. Should there be a history of exposure, or a history of a primary or secondary lesion, good medical judgment indicates a pelvic examination.

Someone may ask if one should rely on the patient's history. Patients are usually truthful if such questions are tactfully put; the physician is not dealing with a reported contact of syphilis on whom the presumption of infection is strong.

What would happen should the physician miss a seronegative primary syphilis? As far as the law is concerned, if he exercised ordinary prudent judgment — which in this situation is being guided by a negative history as stated above, a negative blood test — the answer is quite simple: nothing. The law does not call for any unnecessary or heroic measures.

It is my impression that Dr. Johnson considered the examination clause to be quite new. It is not. The premarital law passed in 1943, and in effect up to May 21, 1950, also required this examination. "Such examination shall be made only to ascertain the presence or absence of evidence of syphilis, and shall include a serological test for syphilis." The 1943 law states specifically the examination "shall include a serological test for syphilis."

Three major items are new in the 1950 law:

Massachusetts will accept the physical-examination report of any physician in the United States, its territories, medical officers of the armed forces and Public Health Service and Canadian physicians provided that the blood sample has been examined by a laboratory of any state health department, territory of the United States, District of Columbia, New York City, armed forces and Public Health Service Laboratories and the Provincial Laboratories of Canada.

The new law requires persons with communicable syphilis to receive treatment prior to marriage.

The certificates of other states are accepted under certain conditions and provided their laws are compatible with those of Massachusetts.

It is hoped that this brief explanation will satisfactorily answer the questions raised, and should any further problems arise, physicians are cordially invited to communicate with the Department.

Nicholas J. Fiumara, M.D., M.P.H., *Director*
Division of Venereal Diseases
Massachusetts Department of Public Health

X-RAY THERAPY OF LYMPHOMA

To the Editor: In the discussion of Case 36422 in the October 19 issue of the *Journal*, Dr. Walter Bauer states that he is "not convinced that any type of lymphoma was ever cured by x-ray therapy, nor . . . that such treatment prolongs life, except in patients with complications affecting vital functions." The term "cure" is not applicable to lymphosarcoma, since patients who are free from clinical evidence of disease after x-ray therapy or surgery may suddenly manifest active tumor foci. The statement that x-ray therapy does not prolong life, except in patients with complications affecting vital functions, is contradicted by a comparison of the survival of treated and untreated patients, in whom these functions were not directly affected.

In Portmann's *Clinical Therapeutic Radiology*, published by Nelson, pp. 545-571, Lenz, Wells and Stout report the following experience at the Presbyterian Hospital, New York City. Of 242 patients receiving x-ray therapy for lymphosarcoma between 1919 and 1942, 22.6 per cent were free from clinical evidence of lymphosarcoma five years and 19 per cent ten years after treatment. Twenty-seven of the 50 five-year survivors had no other treatment except biopsy and x-ray therapy. In the remaining 23 x-ray therapy was preceded by partial and in a few by what was supposed to be complete excision. This proportion of five-year survivors, free from clinical evidence of disease, is certainly greater than the expected survival of untreated patients with lymphosarcoma.

In this series, improvement in survival was chiefly noted in cases in which the disease did not affect vital functions. For instance, none of the 11 patients with primary mediastinal lymphosarcoma receiving x-ray therapy survived five years after treatment. On the other hand, 44 patients with such nonvital localizations as the skin, orbit, tonsil, nasopharynx and cervical, axillary and inguinal lymph nodes were symptom-free at the end of that period.

Surgical claims of long survival are usually complicated by the use of post-operative x-ray therapy, and it is difficult

to decide whether one or the other therapy is responsible for the results.

It would be unfortunate if patients with lymphosarcoma were to be deprived of the benefit of x-ray therapy as the unintentional result of Dr. Bauer's statement, and I therefore take the liberty of calling this evidence to your attention.

MAURICE LENZ, M.D.

New York City

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Manual of Cardiology. By Thomas J. Dry, M.A., M.B., Ch.B., M.S. in medicine, associate professor of medicine, University of Minnesota Medical School (Mayo Foundation), and consultant in section on cardiology, Mayo Clinic. Second edition. 12°, cloth, 355 pp., with 97 illustrations. Philadelphia: W. B. Saunders Company, 1950. $5.00.

This manual, first published in 1943, has been thoroughly revised. Material has been added, and old material deleted. There is a new chapter on heart disease in relation to pregnancy, anesthesia and surgical operations. The small volume is well published.

Postgraduate Gastroenterology: As presented in a course given under the sponsorship of the American College of Physicians in Philadelphia, December, 1948. Edited by Henry L. Bockus, M.D., professor of gastroenterology, University of Pennsylvania School of Medicine. 8°, cloth, 670 pp., with 258 illustrations. Philadelphia: W. B. Saunders Company, 1950. $10.00.

During this short course of one week, various phases of gastroenterology were presented, mostly in the form of symposiums, to which were added three periods of case presentations and clinical conferences. The topics included diagnosis and treatment of esophageal disorders, gastric secretion and gastric analysis, application of neuropsychiatry to gastrointestinal problems, secondary gastrointestinal disorders, including allergy and abdominal symptoms of endocrinal origin, the physiology of the pancreas, abdominal pain, diagnosis and treatment of diseases of the liver, nonspecific enteritis and enterocolitis, intestinal obstruction, jaundice and colonic diseases. Fifty-three physicians contributed to the volume or taught in the course. The most up-to date views are presented in the various short articles. The volume is well published in every way and should be in all collections, public and private, on the subject.

Surgical Treatment for Abnormalities of the Heart and Great Vessels. By Robert E. Gross, M.D., William E. Ladd Professor of Child Surgery, Harvard Medical School. Second printing. 8°, cloth, 73 pp., with 36 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.00. (Publication No. 3, American Lecture Series; A monograph in American lectures in surgery.)

This is a second printing of the Beaumont Lecture delivered in 1946. The subject is well covered, and a bibliography of eighty-four pages is appended to the text. The absence of an index is noted.

NOTICES

ANNOUNCEMENTS

Dr. Christopher L. Landry announces the opening of an office for the practice of neurological surgery at 520 Commonwealth Avenue, Boston.

Dr. Edward F. McGrath announces the opening of an office at the Peabody Chambers, 195 Ashmont Street, Dorchester, for the practice of pediatrics.

Dr. Orvar Swenson announces the removal of his office from the Children's Hospital to the Boston Floating Hospital, 20 Ash Street, Boston, for the practice of pediatric surgery.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present a lecture as part of its evening lecture series in the new Cheever Amphitheater of the Hospital on Tuesday, December 12, at 7 p.m.

The program will consist of a two-part panel. Part 1 "The Art of Practice," will be presented by Dr. Eugene G. Boss, of Springfield, Massachusetts. Part 2, "The Art of Testifying in Court," will be presented by Dr. Richard Ford, of the Department of Legal Medicine at Harvard Medical School.

All interested persons are invited to attend.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the staff of the Peter Bent Brigham Hospital at the New England Mutual Hall, 225 Clarendon Street, Boston, on Monday, December 18, at 8 p.m., Dr. Samuel A. Levine presiding.

PROGRAM

Pathological Physiology of Mitral Stenosis including Calculation of the Size of the Mitral Orifice. Drs. Richard Gorlin and Lewis Dexter.

Changes in the Dynamics of the Circulation following Mitral-Valve Surgery. Drs. Benjamin Lewis, Florence W. Haynes and Dwight E. Harken.

Short PR and Normal QRS Intervals with Paroxysmal Rapid Heart Action. Drs. Bernard Lown, William F. Ganong and Samuel A. Levine.

Significance of Postextrasystolic T-Wave Changes. Drs. Harold D. Levine and Bernard Lown.

The "Chair" Treatment of Acute Coronary Thrombosis. Drs. Samuel A. Levine and Bernard Lown.

Interested physicians and medical students are cordially invited to attend. (*Please note place of meeting.*)

ROBERT BRECK BRIGHAM HOSPITAL

Starting Thursday, December 7, Grand Rounds will be held at the Robert Breck Brigham Hospital, Parker Hill Avenue, Boston, every Thursday morning, rather than every other Thursday, from 9 to 10 o'clock with the exception of holidays or previous notification to the contrary. All doctors and medical students are cordially invited to attend.

SPRINGFIELD ACADEMY OF MEDICINE

The next meeting of the Springfield Academy of Medicine will be held in the Woman's Club Building, 43 Spring Street, on December 12 at 8:30 p.m. Dr. John W. Raker will speak on the subject "Fluid and Electrolyte Balance."

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 2–23. Springfield Hospital. Page 842, issue of November 23.

DECEMBER 9. American Federation for Clinical Research. Page 680, issue of October 26.

DECEMBER 12. Harvard Medical Society. Page 841, issue of November 23.

DECEMBER 12. Boston City Hospital House Officers' Association. Notice above.

DECEMBER 12. Springfield Academy of Medicine. Notice above.

DECEMBER 13. Rhode Island Medical Society. Page 842, issue of November 23.

DECEMBER 13. New England Conferences on Allergy and Related Subjects. Page 898, issue of November 30.

DECEMBER 14. Treatment of Hyperthyroidism, Especially with Radioactive Iodine. Dr. Earle Chapman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

DECEMBER 18. Hartford Medical Society. Page 680, issue of October 26.

DECEMBER 18. New England Cardiovascular Society. Notice above.

DECEMBER 20. Greater Boston Medical Society. Page 898, issue of November 30.

JANUARY 3. Hampshire District Medical Society. Page 170, issue of July 27.

(*Notices concluded on page xv*)

NOTICES (*Concluded from page 938*)

JANUARY 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

JANUARY 23. Norfolk District Medical Society. Page 629, issue of October 19.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.

MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.

APRIL 9–13. American College of Physicians. Page 296, issue of June 15.

APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.

MAY 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 24–26. American Goiter Association. Columbus, Ohio.

OCTOBER 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

District Medical Societies

HAMPSHIRE

JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

JANUARY 23.
FEBRUARY 27.
MARCH 27.
APRIL 24.
MAY 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

Calendar of Boston District for the Week Beginning Thursday, December 14

THURSDAY, DECEMBER 14

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*9:00–11:00 a.m. Medical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, DECEMBER 15

*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

SATURDAY, DECEMBER 16

*9:00–10:00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

MONDAY, DECEMBER 18

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*8:00 p.m. New England Cardiovascular Society. New England Mutual Hall, 225 Clarendon Street, Boston.

TUESDAY, DECEMBER 19

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, DECEMBER 20

*9:00–10:00 a.m. Pediatric Pathological Conference. Joseph H. Pratt Diagnostic Hospital.
*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

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